A Phase 1b/2 Study of the Oral CDK4/6 Inhibitor LEE011 (Ribociclib) in Combination with Docetaxel plus Prednisone in Metastatic Castration Resistant Prostate Cancer

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Protocol Signature Page
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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Investigational Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

_____
UCSF Principal Investigator / Study Chair

_____
Printed Name

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Signature Date

Title	**A Phase 1b/2 Study of the Oral CDK4/6 Inhibitor LEE011 (Ribociclib) in Combination with Docetaxel Plus Prednisone in Metastatic Castration Resistant Prostate Cancer**
Patient Population	Patients with metastatic castration resistant prostate cancer and prior resistance to abiraterone, enzalutamide, ARN-509, or the combination.
Rationale for Study	Prostate cancer is the second leading cause of cancer death in the United States.[1] Although most advanced prostate cancers are initially responsive to androgen ablation therapy, eventually all of these tumors become refractory to androgen deprivation. In the metastatic castration-resistant setting, the widespread introduction of more potent and complete androgen signaling inhibition with abiraterone and enzalutamide has increasingly shifted the landscape of advanced prostate cancer towards an aggressive phenotype with frequent histopathological evidence of neuroendocrine differentiation.[2] The clinical features of this lethal subset of disease are characterized by frequent visceral and widespread osseous metastases and limited responsiveness to androgen signaling inhibition. The current standard of care in this setting remains docetaxel-based chemotherapy, which provides a modest improvement in survival outcomes compared with older chemotherapy regimens.[3] Prior efforts to combine targeted therapies with docetaxel to improve overall survival in metastatic castration-resistant prostate cancer (mCRPC) have not met with success.[4-11] This may be in part be related to lack of biomarker enrichment to select the patients with tumors most dependent on the drug target to guide rationale clinical trial design. Emerging studies implicate up-regulation of cell cycle progression via MYC activation as a key driver of the increased proliferative activity observed with progression to an aggressive phenotypic mCRPC. Pre-clinical studies have demonstrated that cyclin dependent kinases 4/6 (CDK 4/6) are direct transcriptional targets of MYC that mediate accelerated progression through the cell cycle to drive prostate tumor growth.[12] Inhibition of CDK 4/6 in a prostate cancer cell line resistant to enzalutamide, has demonstrated potent arrest of cellular proliferation.[13] Prior pre-clinical data in other MYC-driven tumor subtypes (triple negative breast cancer) indicate synthetic lethality with CDK inhibition in combination with taxane-based chemotherapy[14], and an ongoing phase 1 study of CDK inhibition in combination with paclitaxel suggests the combination is tolerable. The current study is designed to determine the MTD of ribociclib, a potent CDK 4/6 inhibitor) in combination with docetaxel, and in the phase 2 portion of the study, to assess its efficacy in mCRPC patients with prior resistant to abiraterone and/or enzalutamide. The integration correlative biomarker studies, including the use of tumor and "liquid" biopsies to identify Rb1 status and presence of MYC pathway activation, along with metabolic imaging of MYC transcriptional activity, may potentially identify those tumors most 'addicted' to MYC signaling and therefore the most likely to achieve therapeutic benefit with inhibition of CDK 4/6, a key downstream mediator of MYC-driven up-regulation of cell cycle progression.
Primary Objectives	<u>Phase 1b:</u> To determine the safety profile, maximally tolerated dose (MTD), and recommended phase 2 dose of ribociclib in combination with docetaxel plus prednisone in patients with mCRPC. <u>Phase 2:</u> To determine the 6-month radiographic progression-free survival rate with the combination of ribociclib, docetaxel, and prednisone in patients with mCRPC.

Secondary Objectives	• To determine the median radiographic progression-free survival with the combination of ribociclib, docetaxel, and prednisone in patients with mCRPC. • To determine the objective response rate and median duration of response among patients with measurable disease at baseline. • To determine the PSA response proportion and time to PSA progression. • To characterize the safety profile of ribociclib in combination with docetaxel. • To determine if there is evidence of drug-drug interaction between docetaxel + prednisone with ribociclib.
Correlative Objectives	• To determine whether baseline or percent change from baseline in gallium citrate uptake on PET scan is associated with clinical outcomes (Optional - UCSF Patients Only). • To determine whether genomic assessment of MYC pathway activation (MYC amplification or overexpression, Rb1 deletion, cyclin D/E and CDK 4/6 overexpression) assessed within metastatic tumor tissue, circulating tumor cells, and/or cell-free circulating tumor DNA is predictive of clinical outcomes with the combination of ribociclib plus docetaxel. • To determine whether MYC activation score as determined by validated expression signature can distinguish those with and without clinical benefit with ribociclib in combination with docetaxel. • To use an unbiased approach with integration of clinical, genomic, and proteomic data (Differential Pathway Signature Correlation; DiPSC) to define a signature associated with response to taxane + CDK4/6 inhibition in mCRPC.

1 BACKGROUND

1.1 Overall Study Rationale

Prostate cancer is the second leading cause of cancer death in the United States.[1] Although most advanced prostate cancers are initially responsive to androgen ablation therapy, eventually all of these tumors become refractory to androgen deprivation. In the metastatic castration-resistant setting, the widespread introduction of more potent and complete androgen signaling inhibition with abiraterone and enzalutamide has increasingly shifted the landscape of advanced prostate cancer towards an aggressive phenotype with frequent histopathological evidence of neuroendocrine differentiation.[2] The clinical features of this lethal subset of disease are characterized by frequent visceral and widespread osseous metastases and limited responsiveness to androgen signaling inhibition. The current standard of care in this setting remains docetaxel-based chemotherapy, which provides a modest improvement in survival outcomes compared with older chemotherapy regimens.[3] Prior efforts to combine targeted therapies with docetaxel to improve overall survival in metastatic castration-resistant prostate cancer (mCRPC) have not met with success.[4-11] This may in part be related to lack of biomarker enrichment to select the patients with tumors most dependent on the drug target to guide rationale clinical trial design.

Emerging studies implicate up-regulation of cell cycle progression via MYC activation as a key driver of the increased proliferative activity observed with progression to an aggressive phenotypic mCRPC. Pre-clinical studies have demonstrated that cyclin dependent kinases 4/6 (CDK 4/6) are direct transcriptional targets of MYC that mediate accelerated progression through the cell cycle to drive prostate tumor growth.[12] Inhibition of CDK 4/6 in a prostate cancer cell line resistant to enzalutamide, has demonstrated potent arrest of cellular proliferation.[13] Prior pre-clinical data in other MYC-driven tumor subtypes (triple negative breast cancer) indicate synthetic lethality with CDK inhibition in combination with taxane-based chemotherapy[14], and an ongoing phase 1 study of CDK inhibition in combination with paclitaxel suggests the combination is tolerable.

The current study is designed to determine the MTD of ribociclib, a potent CDK 4/6 inhibitor) in combination with docetaxel, and in the phase 2 portion of the study, to assess it's efficacy in mCRPC patients with prior resistance to abiraterone and/or enzalutamide. The integration correlative biomarker studies, including the use of tumor and “liquid” biopsies to identify Rb1 status and presence of MYC pathway activation, along with metabolic imaging of MYC transcriptional activity, may potentially identify those tumors most ‘addicted’ to MYC signaling and therefore the most likely to achieve therapeutic benefit with inhibition of CDK 4/6, a key downstream mediator of MYC-driven up-regulation of cell cycle progression.

1.2 Rationale for Targeting Cell Cycle Progression in Advanced Prostate Cancer

Up-regulation of cell cycle progression is a frequent molecular driver of aggressive phenotype metastatic CRPC. Loss of the tumor suppressor PTEN is observed in 50-90% of CRPC tumors, leading to downstream activation of effectors of the PI3K pathway, including cyclin D, a key driver of G1 to S phase cell cycle progression.[15] Transdifferentiation towards a neuroendocrine phenotype has recently been molecularly characterized as an MYCN oncogene-driven variant in both pre-clinical models and patient-derived cancer tissue.[16] The discovery of MYC overexpression in treatment-emergent NEPC has direct implications for targeting the cyclin-dependent kinase (CDK) pathway in this disease setting, given the direct transcriptional regulation of CDK 4/6 via MYC activation. A recently reported PTEN-knockout transgenic model of prostate cancer identified MYC overexpression upregulation as a key driver of tumor progression.[15] In a landmark translational study of the prostate cancer genome, 74% of human CRPC tissue samples displayed alteration of Rb signaling, with overactivation of CDK2 in 21% of cases and Rb1 loss in 37% of cases.[16] In a previous study of MDV3100-resistant cancer cell lines, gene set

enrichment analysis identified significant up-regulation of genes involved in cell cycle progression and E2F1 activation.[13] Most contemporarily, ours and others data indicates progressive enrichment of MYC amplification as a driver of prostate cancer progression, with amplification detected in 16% of primary prostate adenocarcinomas in the TCGA database, ~ 25-30% of pre-abiraterone/enzalutamide mCRPC tumors, and over 80% of abiraterone-resistant mCRPC tumors from the ongoing UCSF mCRPC biopsy program (preliminary data, unpublished, CC#125519).

The application of CDK inhibitors has shown preliminary evidence of substantial anti-tumor activity in prostate cancer models, in particular those with androgen-independent growth upon resistance to androgen signaling inhibitors. In a panel of bicalutamide-resistant, androgen-independent prostate cancer cell lines, CDK2 inhibition was able to restore sensitivity with a potency that was comparable to that of LNCaP androgen-sensitive cell lines.[17] More recently, CDK 4/6 inhibitors including ribociclib have been shown to have significant anti-proliferative effects in MDV3100 (enzalutamide)-resistant cancer cell lines bearing either mutant F876L mutant- or wild type androgen receptor[13] (**Figure 1)**. The anti-tumor activity of CDK inhibitors has additionally been demonstrated in other MYC-driven cancers. Synthetic lethality with CDK inhibition was demonstrated in multiple triple negative breast cancer lines which demonstrate up-regulated C-MYC signaling.[14] Prior clinical studies with cell cycle inhibitors in mCRPC, include flavopiridol, have demonstrated modest activity[18]; however these agents were neither potent nor selective inhibitors of CDK 4/6. It is hypothesized that potent CDK inhibition with ribociclib will have substantial additive or synergistic activity with docetaxel in mCRPC.

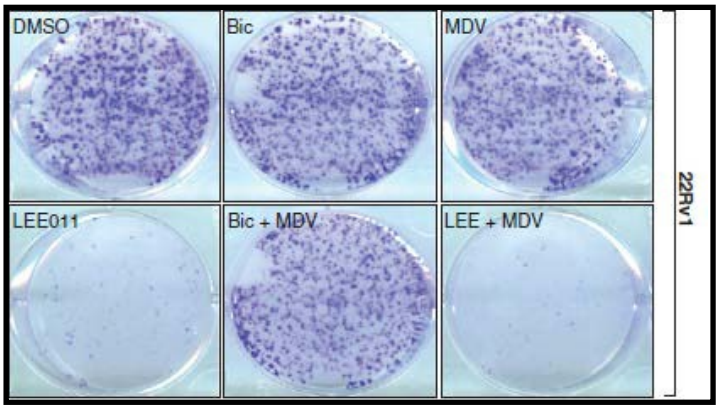


Figure 1. Ribociclib significantly inhibits colony proliferation in the 22Rv1 enzalutamide (MDV) and bicalutamide (bic)-resistant prostate cancer cell line. Figure from Korpal M, et al. Cancer Discovery 2013;3(9):1030-1043.

1.3 Rationale for Combination of CDK 4/6 Inhibitor With Taxane Chemotherapy

Taxane-based chemotherapy and CDK inhibitors have demonstrated synergistic activity in multiple independent studies, which may be related to blockade of cell cycle progression at separate phases of the cell cycle (M and G1→S phases respectively). In vitro studies have demonstrated synergy when cell cycle inhibitors like flavopiridol and purvalanol are administered with paclitaxel and docetaxel.[14] Recently, the Goga lab at UCSF has demonstrated synergistic activity in TNBC cell lines (BT549, MDA-MB-231, HCC1143) treated with dinaciclib and paclitaxel therapy.[14] In an ovarian cancer xenograft model, co-administration of docetaxel and dinaciclib demonstrated synergistic activity compared to either agent given alone. Similar synergistic activity with taxanes has been demonstrated with other CDK-inhibitors including flavopiridol, NU6410, and purvalonol. A phase 1b study of dinaciclib in combination with weekly paclitaxel (NCT01676753) being conducted at UCSF has demonstrated preliminary evidence of an acceptable safety profile with efficacy analyses ongoing. The above findings, coupled with the fact that docetaxel-based chemotherapy remains the standard of care for metastatic CRPC with aggressive phenotypic features and/or prior resistance to androgen signaling inhibition, provide a strong rationale to pursue the combination of CDK4/6 inhibition in combination with docetaxel in mCRPC.

1.4 Summary of Ribociclib Pre-Clinical and Clinical Safety, PK, and Efficacy Data

In vitro Pharmacology:

Ribociclib inhibits the CDK4/CCND1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (IC50) values of 0.01 and 0.039 μM in biochemical assays, respectively. In Jeko-1 cells, the compound inhibits CDK4/6-dependent pRb phosphorylation with an average IC50 of 0.06 μM. Consistent with the observed inhibition of pRb phosphorylation, ribociclib also inhibited G1 to S phase cell cycle progression in Jeko-1 cells as judged by both the inhibition of bromodeoxyuridine (BrdU) uptake (IC50 of 0.1 μM) and fluorescence activated cell sorting (FACS) analysis (half-maximal increase in cells in G1 at 0.11 μM).

The effect of ribociclib on pRb phosphorylation, BrdU uptake and cell cycle progression has been assessed in > 40 cell lines derived from hematological, esophageal, liposarcoma and breast cancers. In pRb+ cell lines ribociclib inhibits pRb phosphorylation with a median IC50 value of 0.275 μM (range: 0.06 to 8.8 μM). Similarly, ribociclib interferes with G1 to S phase cell cycle progression in these cells as determined by either BrdU uptake or FACS analysis with a median IC50 value of 0.46 μM.

In vivo Pharmacology:

Ribociclib was well-tolerated in mice and rats with body weight loss not exceeding 12.5% at doses up to 250 mg/kg, qd, po. No significant changes in blood chemistry readouts were observed after 28 days of dosing. However, myelosuppression was observed and correlated with pRb phosphorylation inhibition.

Treatment with ribociclib resulted in tumor regression in the Jeko-1 MCL xenograft model at doses greater than or equal to 75 mg/kg, qd, po. In vivo pharmacokinetic (PK)/PD studies demonstrated dose-related inhibition of pRb phosphorylation in tumors, with continuous dosing over at least 3-5 days being required to achieve optimal target inhibition. In male nude rats a PK/PD/efficacy study indicated that plasma levels corresponding to approximately 0.5 - 4 μM over a 24 h dose interval are sufficient to obtain near complete inhibition of pRb phosphorylation and complete regression in the Jeko-1 MCL xenograft model.

Non-clinical Safety and Toxicology:

In vivo cardiac safety studies demonstrated a signal for QT prolongation with the potential to induce incidences of premature ventricular contractions (PVCs) at higher exposure levels. The effects of ribociclib on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition. An increased number of ovarian corpora lutea was observed in a single female dog at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of ribociclib (arrest of estrous cycle). The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of ribociclib. Inflammatory changes in the lungs of dogs were considered secondary to aspiration of test-article and are indicative of the irritant potential of the formulated test-article in the respiratory tract. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. In rats, the changes seen in the bone marrow and hematology demonstrated a clear tendency towards reversibility. All other findings fully reversed. In dogs, the changes seen in the testes and lungs demonstrated a clear trend

towards reversibility and all the other changes were fully reversible. However, it can be expected that after a prolonged recovery time all findings would have totally reversed.

Reproductive studies have demonstrated ribociclib induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rabbits.

Non-clinical Pharmacokinetics and Metabolism:

Following intravenous [i.v.] dosing, ribociclib showed high CL in the mouse, rat, dog and monkey compared to hepatic blood flow. The volume of distribution at steady-state was large across species and the terminal elimination half-life (T1/2) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h). After oral administration to male rats, 48 to 84% of a radiolabeled dose of ribociclib was absorbed. Bioavailability was low to moderate in rat (10 to 65%) and cynomolgus monkey (10 to 23%), and moderate in mouse (65%) and dog (64%). Following oral administration, Tmax occurred between 2 to 4 h across species. Gender-dependent toxicokinetics were observed in rats with higher exposure to ribociclib in males as compared to females and with higher exposure to the metabolite, LEQ803. Plasma protein binding was moderate and showed no major concentration dependency. Free fraction in plasma ranged from 20 to 32%.

LEQ803 (N-demethylation) was a prominent metabolite found in rat, monkey and human hepatocytes, and the only metabolite formed in dog hepatocytes. This metabolite retains some pharmacologic activity and interacts with hERG channels in vitro. Traces of two potential unique human metabolites were detected in hepatocytes. In mice, rats, monkey and human, GSH-adducts were detected however these were not seen in plasma or excreta from the rat ADME study. Results from the ADME (male rats) study showed that 3H-components were predominantly excreted with bile (61.4% of dose). Minor urinary excretion was observed (5.44% of dose after p.o. to 10.1% of dose after i.v.). The majority of the administered dose (87.3%) was excreted within 24 h via urine, feces (enteric secretion) and bile.

Drug-drug interaction: Oxidative metabolism of ribociclib is dominated by CYP3A4 with a minor contribution of about 20% by flavin containing monooxygenase-3 (FMO3). ribociclib is a low-affinity substrate of P-gp (MDR1). ribociclib is a time-dependent CYP3A4 inhibitor (KI = 5 μM, kinact = 0.0245 min-1) and a reversible inhibitor of CYP1A2 (Ki = 16 μM). No PXR-mediated CYP3A4 induction was observed. ribociclib was found to inhibit MDR1 (IC50 = 143 μM), MXR (IC50 = 24 μM), and human BSEP (IC50 = 4.7 μM), but not rat or dog BSEP. The elimination of ribociclib may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. ribociclib may inhibit CYP3A4, CYP1A2, BSEP, and MXR depending on the dose and ribociclib concentrations achieved in vivo.

Clinical Studies:

In single agent trials, a total of 179 patients have been treated: 132 in study CLEE011X2101 (in a Caucasian population, including 85 in the dose escalation), 15 in CLEE011X1101 (in Japanese patients, all in the dose escalation) and 32 in CLEE011X2102 (in patients under the age of 21 years, all in the dose escalation). A total of 18 patients presented toxicities meeting the dose limiting toxicity (DLT) criteria (10 in CLEE011X2101, 4 in CLEE011X1101 and 4 in CLEE011X2102): these consisted of Grade 3 stomatitis, Grade 3 pulmonary embolism, Grade 3 hyponatremia, prolonged Grade 3/4 neutropenia (x2), prolonged Grade 2 elevated creatinine, Grade 4 thrombocytopenia (x5), Grade 3 asymptomatic QTcF prolongation with Grade 3 neutropenia, Grade 4 febrile neutropenia, Grade 3 febrile neutropenia (x2), Grade 3 electrocardiogram QT prolonged, Grade 3 fatigue, and Grade 3 asymptomatic QTcF prolongation with grade 4 neutropenia.

The maximum tolerated dose (MTD) and recommended dose for expansion (RDE) from study CLEE011X2101 were declared as 900 mg qd and 600 mg qd on a 3 weeks on/1 week off schedule, respectively. At the RDE, the most common (in at least 2 patients) adverse events (AEs) related to study treatment were (all grades, Grade 3/4): neutropenia (46.3%, 28.4%), leukopenia (46.3%, 19.4%), nausea (44.8%, 1.5%), thrombocytopenia (34.3%, 9%), fatigue (32.8%, 3%), anaemia (28.4%, 3%), diarrhoea (26.9%, 3%), lymphopenia (22.4%, 17.9%), electrocardiogram QT prolonged (9%, 0%), hyponatremia (3%, 1.5%), and febrile neutropenia (1.5%, 1.5%). Asymptomatic grade 2 QTc prolongation was observed with increasing frequency starting at 600 mg with grade 3 prolongation in 2 patients (3%). The majority of all reported adverse events were mild or moderate (grade 1-2) and reversible. There have been no reported deaths related to single agent ribociclib.

Paired skin biopsies from 55 patients treated with ribociclib at doses ranging from 50 to 900 mg and paired tumor biopsies from 20 patients (16 patients at 600 mg, 2 patients at 900 mg, and 1 patient each at 70 and 750 mg) were assessed for changes in Ki67 and pRb levels. Preliminary results indicate the following: in skin biopsies, reductions in Ki67 from baseline were observed across all dose levels with a more consistent trend from 400 mg onwards; in tumor biopsies, reductions in Ki67 from baseline were observed in 18/20 patients; however, limited samples and varied tumor types prevent conclusions about any dose-response relationship from being drawn. Changes in pRb were not significant or consistent in either skin or tumor samples, possibly due to varied tumor types.

Preliminary data for clinical activity from study CLEE011X2101 show that out of 114 evaluable patients, 3 partial responses were seen at the 600 mg qd dose level: one in a BRAF/NRAS wild type, CCDN1 amplified melanoma patient, one in a CDKN2A loss head and neck acinar carcinoma patient, and one in an ER+/HER2-, PIK3CA mutant, CCDN1 amplified breast cancer.

Following oral dosing, ribociclib was rapidly absorbed with median Tmax ranging from 1 to 5 hours. ribociclib plasma exposure exhibited slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady-state was generally reached by Day 8 and the mean effective T1/2 based on accumulation ratio (i.e., T1/2,acc) ranged from 15.9 to 32.6 hours across the dose range tested. The accumulation ratio based on AUC obtained in a dosing interval (Racc) across the studied doses ranged from 1.55 to 2.52.

The MTD of single agent ribociclib is 900 mg qd with a 3 weeks on/1 week off schedule. The RP2D for future development of single agent ribociclib dosing is 600 mg qd with a 3 weeks on/1 week off schedule which has an acceptable safety profile, lower risk for QT prolongation, adequate exposures, and preliminary evidence of clinical activity.

1.5 Summary of Docetaxel Mechanism of Action, Efficacy, Safety and Pharmacokinetics

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

The most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation,

anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

Every 3 week docetaxel at 75 mg/m^2 in combination with prednisone 5 mg BID has been evaluated in a randomized phase 3 study in metastatic castration-resistant prostate cancer. In the TAX327 phase 3 study, every 3 week docetaxel + prednisone prolonged median survival from 16.5 months (95% CI 14.4-18.6) for patients treated with standard of care mitoxantrone + prednisone to 18.9 months (95% CI 17.0-21.1) in patients treated with every 3 week docetaxel (p = 0.009). Weekly docetaxel was also evaluated in this trial and displayed a numerically prolonged survival compared to mitoxantrone (17.4 versus 16.5 months) which did not meet statistical significance (p = 0.36). The results of this trial led to the FDA approval of docetaxel plus prednisone in mCRPC and established every 3 week docetaxel as the standard first-line chemotherapy in mCRPC.

1.6 Rationale for the Starting Dose Level and Dose Schedule of Docetaxel and Ribociclib

The starting dose of docetaxel is fixed for all dose levels at 75 mg/m^2 every 3 weeks. Docetaxel dosed at 75 mg/m^2 every 3 weeks was shown to be superior to weekly docetaxel with respect to efficacy outcomes in a prior randomized phase 3 study. If excess toxicity (particularly hematologic) is observed at the first dose level of the combination of ribociclib plus docetaxel, an alternative dosing schema may be pursued with 60 mg/m^2 docetaxel every 3 weeks and/or weekly docetaxel dosing upon review of safety results with Principal Investigator. Both 60 mg/m^2 every 3-week docetaxel as well as weekly docetaxel have demonstrated efficacy and less hematologic toxicity compared with 75 mg/m^2 every 3 week docetaxel dosing.

The starting dose of ribociclib in the Phase 1b portion of the study will be 200 mg/day days 2-14 of every 21 day cycle. The rationale for starting ribociclib on day 2 as opposed to day 1 of the treatment cycle stems from prior pre-clinical observations that synergistic activity is observed with taxane plus CDK4/6 inhibition when taxane treatment is delivered prior to CDK inhibition.[14] A similar sequential dosing strategy was successfully implemented in a phase 1b study of paclitaxel in combination with the CDK inhibitor dinaciclib in patients with triple negative breast cancer.

The starting dose of ribociclib (200 mg/day) is predicted to achieve serum concentrations above the level necessary for CDK 4/6 inhibition based upon pre-clinical studies (IB). The maximal dose of ribociclib (600 mg/day) to be evaluated in the current study is the recommended single agent phase 2 dose. A schedule of 2 weeks on, 1 week off is based upon the observation from initial clinical studies of ribociclib indicating the onset of cytopenias at approximately day 15 of each treatment cycle, and full recovery after a 7 day treatment break. Preliminary clinical data do not indicate a compromise in disease efficacy with a one week treatment break with ribociclib.

1.7 Rationale for the Correlative Studies

<u>Tissue and Peripheral Blood Assays of MYC Pathway Activation:</u>
Putative resistance and sensitivity markers of CDK 4/6 inhibitors including Rb1 loss (resistance), cyclin D2 overexpression (sensitivity), CDK 4/6 overexpression (sensitivity), MYC overexpression and amplification (sensitivity) will be assessed in an exploratory fashion during the Phase 2 portion of the study to determine whether there are particular indicators of clinical benefit with CDK4/6 inhibition in specific patient populations.

Patients will undergo optional metastatic tumor biopsy prior to day 1 of study treatment during Phase 2 of the study. Preliminary data indicates high rate of evaluable biopsy material from metastatic prostate tumor biopsies, including bone (yield 70-90%). For the UCSF patients undergoing tumor biopsy during Phase 2, the infrastructure from the ongoing clinical study [redacted] will be utilized for tissue

analysis, including RNA sequencing to determine levels of gene expression of MYC pathway elements.

Peripheral blood (all patients) will also be collected for circulating tumor cell (CTC) and cell-free circulating tumor DNA (ctDNA) analysis at Screening (phase 2 only). In past studies, collection of CTCs and cell-free ctDNA has been feasible and results have had reasonable concordance with metastatic tumor tissue.

Gallium citrate PET Imaging (Optional - For UCSF Patients Only)

In considering non-invasive strategies to more expediently investigate the role of MYC in mCRPC, several groups have reported preclinical data showing that a small handful of radiotracers can measure MYC biology by targeting a downstream event regulated by MYC. Among these include radiolabeled transferrin (Tf) adducts, which provide a readout of intracellular MYC activity by detecting expression changes in the transferrin receptor (TFRC), a direct and specific MYC target gene (**Fig. 2A**). When considering clinically available radionuclides to non-invasively quantify MYC transcriptional activity, ^{68}Ga-citrate-based PET possesses a strong rationale to evaluate in this setting: (1) Gallium citrate rapidly and specifically binds transferrin in vivo, providing in turn a quantifiable read-out of transferrin receptor density and therefore MYC transcriptional activity **(Fig. 2B);** (2) As compared with gallium-67, gallium-68 has a much shorter half-life (68 m vs. 3.2 d) and decays primarily by positron emission (^{67}Ga: multiple single photon emission at 93, 184, and 300 keV) allowing higher doses to be injected and shorter imaging studies. ^{68}Ga is readily available from the germanium-68 generator; (3) ^{68}Ga-citrate does not accumulate within the pulmonary parenchyma, allowing for markedly improved sensitivity and specificity in detecting regions of transferrin receptor overexpression (4) ^{68}Ga-citrate imaging has an established pre-clinical and clinical safety and dosimetry record, and is available for clinical use. Indeed, proof-of-concept PET imaging studies in humans have already shown that it can target foci harboring cells with high TFRC expression (e.g. peripheral mononuclear blood cells at sites of infection).[20]

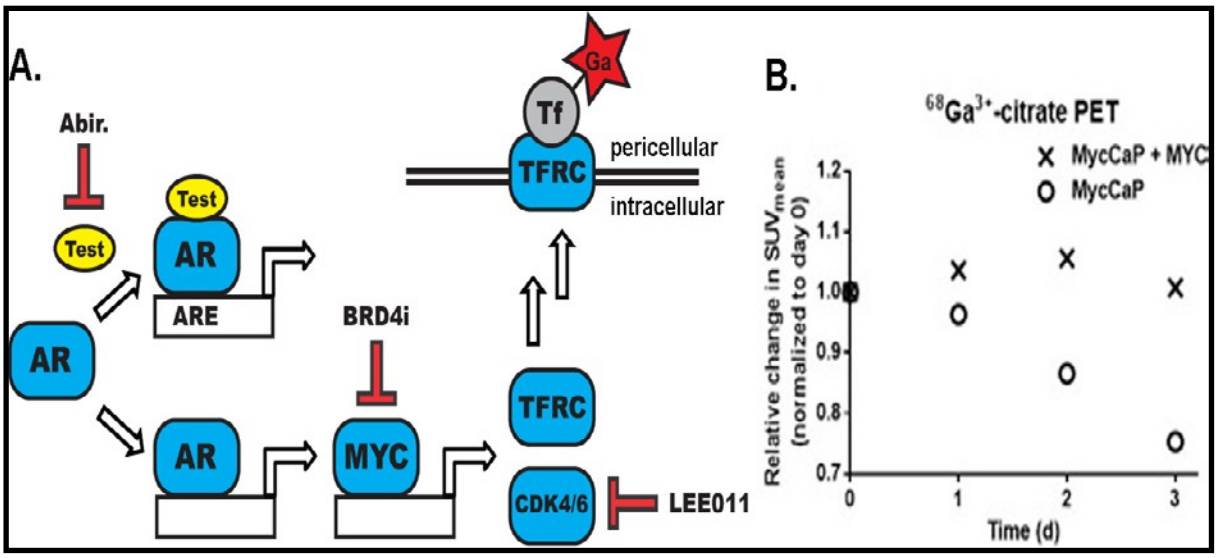


Figure 2: Measuring MYC signaling in prostate cancer with ^{68}Ga-citrate PET. A. A schema summarizing the biological hypothesis of the grant. At left, systemic abiraterone (Abir.) treatment will affect a disease response by inhibiting the production of androgens like testosterone (test.) and preventing the androgen receptor (AR) from performing transcription at androgen response elements (AREs). Alternatively, a subset of disease will escape control by virtue of AR's ability to transcribe MYC in a ligand independent fashion. In addition AR independent MYC expression can override clinical benefit associated with single agent inhibitors of AR. MYC in turn transcribes a large repertoire of target genes responsible for proliferation and survival. Among these are the transferrin receptor (TFRC), an essential regulator of iron homeostasis, and cyclin dependent kinases 4 and 6 (CDK4/6), two of a family of enzymes that regulate cell cycle progression. Diagnostically, we hypothesize that MYC overexpressing tumors will be identified with a Gallium-68 (Ga)/transferrin adduct on the basis of high TFRC expression. Therapeutically, we hypothesize that patients with disease highly avid for gallium-citrate will most demonstrably respond to CDK4/6 inhibition with ribociclib on the basis of an "addiction" to MYC signaling. B. A summary of the region of interest analysis for MYC dependent gallium-68 citrate uptake in mouse prostate cancer xenograft models. Mice were inoculated with MycCaP, a model in which MYC is regulated by ligand activated AR, or MycCaP + MYC, a MycCaP subline that also harbors an additional MYC allele with a constitutive promoter. Castration resulted in a rapid downregulation of gallium-68 citrate uptake in the MycCaP tumor, but no substantial change in uptake for the MycCaP + MYC tumor model. This finding is consistent with the model of MYC regulation of TFRC outlined in A.

2 STUDY OBJECTIVES

2.1 Primary Objectives:

Phase 1b:
To determine the safety profile, maximally tolerated dose (MTD), and recommended phase 2 dose of ribociclib in combination with docetaxel plus prednisone in patients with mCRPC.

Phase 2:
To determine the 6-month radiographic progression-free survival rate with the combination of ribociclib, docetaxel, and prednisone in patients with mCRPC.

2.2 Secondary Objectives:

- To determine the median radiographic progression-free survival with the combination of ribociclib, docetaxel, and prednisone in patients with mCRPC.
- To determine the objective response rate and median duration of response among patients with measurable disease at baseline.
- To determine the PSA response proportion and time to PSA progression.
- To characterize the safety profile of ribociclib in combination with docetaxel.
- To determine if there is evidence of drug-drug interaction between docetaxel + prednisone with ribociclib.

2.3 Exploratory

Objectives:

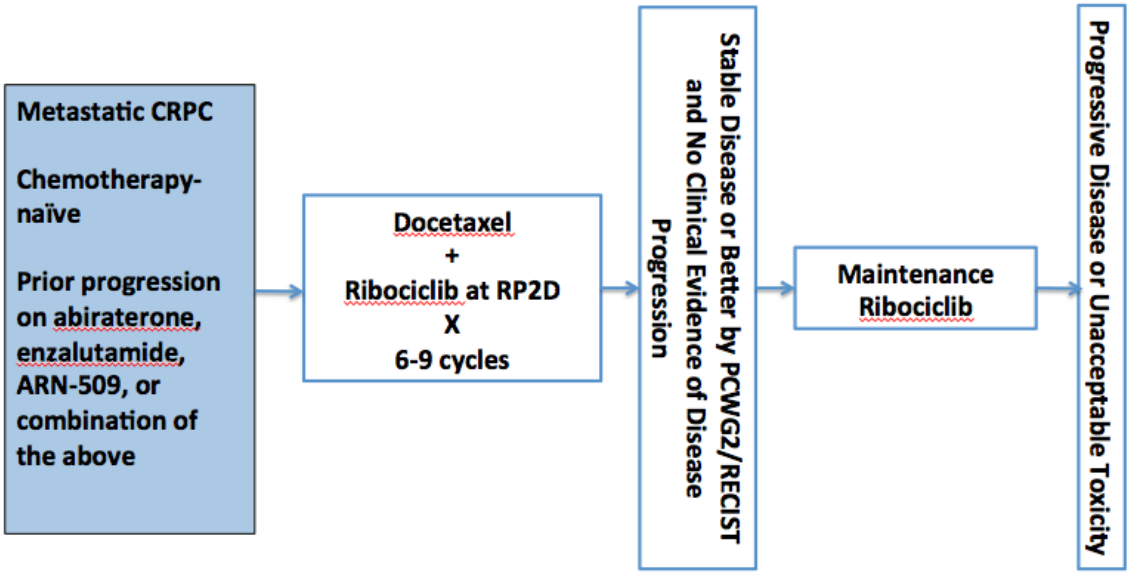
- To determine whether baseline or percent change from baseline in gallium citrate uptake on PET scan is associated with clinical outcomes (For UCSF Patients Only).
- To determine whether genomic assessment of MYC pathway activation (MYC amplification or overexpression, Rb1 deletion, cyclin D/E and CDK 4/6 overexpression) assessed within metastatic tumor tissue, CTCs, and/or cell-free ctDNA is predictive of clinical outcomes with the combination of ribociclib plus docetaxel.
- To determine whether MYC activation score as determined by validated expression signature can distinguish those with and without clinical benefit with ribociclib in combination with docetaxel.
- To use an unbiased approach with integration of clinical, genomic, and proteomic data (Differential Pathway Signature Correlation; DiPSC) to define a signature associated with response to taxane + CDK4/6 inhibition in mCRPC.

3 STUDY DESIGN

3.1 General Study Design

This is a Phase Ib/II open label clinical trial in patients with metastatic castration resistant prostate cancer. The objective of the phase Ib portion of the study is to establish the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of docetaxel and prednisone in combination with ribociclib in escalating oral daily doses in patients with metastatic CRPC with prior resistance to abiraterone and/or enzalutamide who have not undergone prior chemotherapy for metastatic disease. Dose escalation will follow the standard 3+3 design. The initial dosing schedule was chosen to allow patients to be exposed to the most efficacious dosing schedule of docetaxel (75 mg/m2 every 3 weeks). If there is excess toxicity observed with the treatment combination at the first dose level (dose level I), an alternative dosing schema may be pursued with docetaxel 60 mg/m2 every 3 weeks and/or weekly docetaxel treatment (30 mg/m^2 weekly two of every three weeks). Both of these alternative docetaxel dosing schedules have demonstrated activity in mCRPC with decreased risk of cytopenias compared with 75 mg/m2 every 3 week. Intermediate dose levels and/or alternative dosing schedules of ribociclib may be investigated in Phase Ib based on the initial safety data.

The Phase 2 portion (N = 29) of the study is a single arm, two stage, open-label study of ribociclib (dosed at the RP2D and schedule) in combination with docetaxel and prednisone to determine the efficacy and further define the safety of the treatment combination. Patients will be treated with the combination of ribociclib plus docetaxel + prednisone for up to 9 cycles. If there is no evidence of radiographic or clinical disease progression after 9 cycles of protocol therapy, patients may continue on single agent maintenance ribociclib until the time of disease progression. Patients will have the option of starting maintenance ribociclib after 6 cycles of docetaxel if stable disease or better on re-staging scans. The dose of ribociclib used during maintenance will be the same dose as that immediately preceding cessation of docetaxel treatment.



3.2 Inclusion Criteria

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Histologically confirmed prostate cancer. Small cell/neuroendocrine differentiated allowed but not required for study participation.

2. Progressive metastatic prostate cancer (as defined below in Item #5) despite castrate levels of testosterone (< 50 ng/dL).

3. Patients may have either non-measurable disease OR measurable disease

4. Progressive disease during (or within 4 weeks of completion) with abiraterone, enzalutamide, and/or ARN-509 based on any one of the following:

   a. For patients with measurable disease, progression by the RECIST criteria.[13]

   b. PSA evidence for progressive prostate cancer consists of a PSA level of at least 2 ng/ml which has risen on at least 2 successive occasions, at least one week apart. If the confirmatory PSA (#3) value is less (i.e., #3b) than the baseline PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression for the purposes of eligibility.

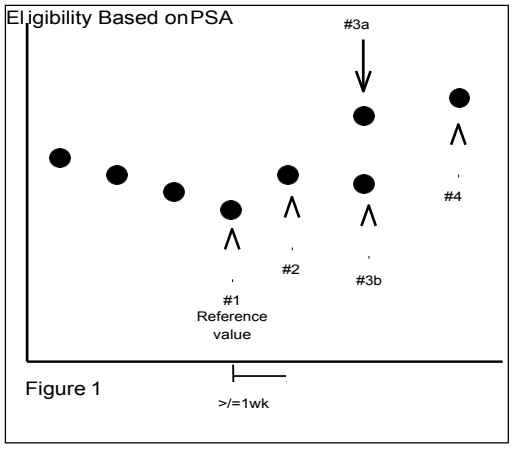


Figure 1

   c. Radionuclide bone scan: At least two new foci consistent with metastatic lesions

5. Testosterone < 50 ng/dL. Patients must continue primary androgen deprivation with an LHRH analogue if they have not undergone orchiectomy.

6. Patients treated with first generation anti-androgen as most recent systemic therapy (bicalutamide, nilutamide) must have at least 4 weeks elapsed from treatment discontinuation to start of protocol therapy with evidence of disease progression by PCWG2 criteria f*ollowing* discontinuation of prior anti-androgen.

7. ECOG Performance Status 0 or 1 (see **Appendix 1**).

8. Patient has adequate bone marrow and organ function as defined by the following laboratory values:
   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L.
   - Platelets $\geq 100 \times 10^9$/L.
   - Hemoglobin ≥ 9 g/dl.
   - Potassium, total calcium (corrected for serum albumin), magnesium and sodium within normal limits for the institution or corrected to within normal limits before first dose of study medication.
   - INR ≤ 1.5 unless on direct thrombin inhibitor at time of study entry.
   - Serum creatinine $\leq$ 1.5mg/dL or estimated creatinine clearance $\geq$ 50 ml/min
   - In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If the patient has liver metastases, ALT and AST <5 x ULN
   - Total bilirubin < ULN; or total bilirubin ≤3.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome.

9. No other systemic therapies for prostate cancer within 28 days or 5 half-lives, whichever is shorter, prior to day 1 of study therapy.

10. Sexually active males must use a condom during intercourse while taking the drug and for 30 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Fertile males must use a condom with spermicide (double barrier method).

11. Age $\geq$ 18 years

12. Written informed consent must be obtained prior to any screening procedures and according to local guidelines.

3.3 Exclusion Criteria

Patients eligible for this study must not meet any of the following criteria:

1. Patient has a known hypersensitivity to ribociclib or any of its excipients including peanuts and soy, or prior treatment with CDK 4/6 inhibitor.

2. Prior chemotherapy for metastatic castration-resistant prostate cancer. Chemotherapy administered in the castration-sensitive setting is allowed provided last dose of chemotherapy was greater than 12 months prior to study entry

3. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated non-melanomatous skin cancer and superficial bladder cancer (including carcinoma-in-situ).

4. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
   - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment

- Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases.
- Baseline screening for CNS metastases is not required unless presence of signs and/or symptoms of involvement

5. Patient is not able to swallow oral medication and/or has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or significant small bowel resection).

6. Clinically significant, uncontrolled heart disease and/or recent events including any of the following:
   - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) or symptomatic pericarditis within 12 months prior to Screening
   - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
   - Patient has a left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) obtained during Screening.
   - History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months of Screening. Patients with rate-controlled atrial fibrillation or flutter are permitted.
   - Bradycardia (heart rate < 50 bpm at rest), by ECG or pulse, at Screening
   - Congenital long QT syndrome or family history of long QT syndrome
   - Any of the following abnormalities on Screening 12-lead ECG:
     - QTcF > 450 msec
     - Bradycardia (heart rate < 50 bpm at rest)
     - Tachycardia (heart rate > 100 bpm at rest)
     - PR interval > 220msec,
     - QRS interval >109 msec
   - Documented cardiomyopathy
   - Systolic blood pressure >160 mmHg or <90 mmHg at Screening

7. AST and/or ALT > 1.5 x ULN with concomitant alkaline phosphatase > 2.5 x ULN

8. Patient receiving any of the following medications (see **Appendix 2**) within 7 days of day 1 of study treatment.
   - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
   - That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
   - That have a known risk to prolong the QT interval or induce Torsades de Pointes.
   - Herbal preparations/medications that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation.

9. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug at a dose greater than the equivalent of 10 mg prednisone/day, or who have not fully recovered from the side effects of such treatment
   a. The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

10. Patient is currently receiving warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, direct thrombin inhibitors, low molecular weight heparin (LMWH) or fondaparinux is allowed.

11. Major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).

12. Patient who has received radiotherapy ≤ 4 weeks prior to starting study drug, and who has not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia), and/or in whom ≥25% of the bone marrow was irradiated.

13. Prior treatment with radiopharmaceutical including radium-223, strontium-89, or samarium-153.

14. Patient has a known history of HIV infection (testing not required)

15. Patient has not recovered from all toxicities related to prior anticancer therapies to NCI-CTCAE version 4.03 to less than or equal to Grade 1 (Exception to this criterion: patients with any grade of alopecia are allowed to enter the study).

16. Patients with chronic liver disease with a Child-Pugh score B or C.

17. Patients with serious intercurrent infections, or nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this therapy.

18. Patients with severe psychiatric illness/social situations that would limit compliance with study requirements in the judgment of study investigator.

19. History of bleeding diathesis.

20. Patient has a history of non-compliance to medical regimen or inability to grant consent

21. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer

4 SUBJECT REGISTRATION AND ENROLLMENT

4.1 Subject Recruitment & Study Sites

Patients will be screened for interest and eligibility by the medical oncologists in the Urologic Oncology Practice at the UCSF Cancer Center and by other participating study sites per their local recruitment and screening practices. Patients to be screened will include those currently followed in the UCSF practices including those referred from outside providers, as well as other participating Study Sites per their local practice.

4.2 Registration Procedures

Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization form/Heath Insurance Portability and Accountability Act

(HIPAA) authorization form. All eligible patients must be centrally registered through the Prostate Cancer Clinical Trials Consortium, LLC (PCCTC). To complete the registration process, the study site must email the signed completed study-specific eligibility checklist, all source documents verifying eligibility, any supporting documents, and the signed informed consent to PCCTC [redacted]. UCSF is the only site exempt from submitting source documents and supporting documents and is only required to submit the signed, completed study-specific eligibility checklist and informed consent to PCCTC. Once the enrollment packet is received and reviewed at PCCTC and if eligibility is confirmed, assignment to treatment can occur and the patient will be enrolled in Medidata Rave®, the Electronic Data Capture (EDC) system for this study. Study Chair will be knowledgeable of all registrations. Participating sites will register patients locally per their Institutional guidelines in addition to central registration with PCCTC. Patients failing to meet all study eligibility requirements will not be registered.

5 SCHEDULE OF ASSESSMENTS

5.1 Pre-treatment Evaluation

5.1.1 Clinical (within 14 days prior to registration)

a. Complete history and physical examination, including height, weight, and baseline evaluation of symptoms, pain and medications
b. Performance Status (ECOG/KPS scale) – **Appendix 8**
c. EKG

5.1.2 Laboratory (within 14 days prior to registration)

a. Complete blood count including differential and platelet count
b. Chemistry panel: Alkaline phosphatase, albumin, total bilirubin, BUN, calcium, creatinine, glucose, LDH, AST, ALT, sodium, potassium, bicarbonate, chloride, magnesium
c. PT/INR + PTT
d. PSA
e. Testosterone level (may be obtained within 28 days prior to registration)
f. CTCs and cell-free ctDNA (Phase 2 only)

5.1.3 Radiographic and Diagnostic Studies (within 42 days of registration)

a. Radionuclide bone scan
b. CT scan of the chest, abdomen and pelvis (with IV contrast if kidney function is adequate. MR abdomen/pelvis is acceptable).
d. MUGA or echocardiogram (may be performed within 42 days of initiating treatment in both Phase 1 and Phase 2)
e. Gallium-citrate PET scan (Optional, UCSF Patients Only - Phase 2 only). PET scan should be performed prior to tumor biopsy (see below)

5.1.4 Tumor biopsy (within 28 days of registration; optional):

Core or excisional biopsy preferred over fine needle aspiration.

5.2 Evaluations during treatment and end-of-treatment

Phase 1b Schedule (N ~ 9-18 evaluable patients):

Study Assessments	Screen[a]	Cycle 1				Cycle 2 and Every Cycle Thereafter	End of Study (within 30 days of last treatment)
		D 1	D2	D8	D15	Day 1	
Informed Consent	X						
Medical History	X						
Physical Examination	X	X	X	X	X	X	X
Concurrent Medications	X	X		X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Weight and Height	X	X				X	X
CBC + Differential[b]	X	X		X	X	X	X
PT/PTT + chemistry panel[b]	X	X		X	X	X	X
Serum PSA	X	X				X	X
Serum testosterone	X						
MUGA or echocardiogram	X						
12-lead ECG[c]	X				X	X	
Pharmacokinetics[d]		X	X				
Tumor Assessment[e]	X					X	X
Docetaxel Administration[f]		X				X	
Neupogen Administration[g]		See Section 6 for schedule					
Ribociclib Administration		Dosed Daily (see Section 6 for schedule)					

a. Screening labs may be used on Cycle 1Day 1 if drawn within 3 days prior to start of treatment.
b. For every 3-week docetaxel dosing schedule, CBC + differential will be measured Days 1, 8, and 15 of Cycle 1, Days 1, 8 (+/- 2 days), and 15 (+/- 2 days) during Cycles 2-3, and then on Day 1 of Cycle 4 and every cycle thereafter. For weekly docetaxel dosing schedule, CBC + differential will be measured on Days 1, 8, and 15 of Cycle 1, Days 1, 8, and 15 (+/- 2 days) during Cycles 2-3, and then on Days 1 and 8 of every cycle thereafter. Chemistry panel as described in **Section 5.1.2.**
c. 12-lead ECG will be performed during Screening, pre-dose Cycle 1 Day 15, pre-dose Cycle 2 Day 1, and on Day 1 of every cycle thereafter (pre-dose).
d. PK assessment schedule:
Ribociclib:
C1D1: Pre-dose, t + 1 hour post dose (+/- 5 min), t + 2 hours post dose (+/- 5 min), t + 4 hours post-dose (+/- 5 min)
C1D2: t + 24 hours post-dose (+/- 1 hour)
Docetaxel:
C1D2: t + 24 hours post-dose (+/- 1 hour)
Please see **Appendix 4** for additional details
e. Tumor assessment will be completed at the completion of every 3 treatment cycles (9 weeks). Tumor assessment to include CT chest/abdomen/pelvis (with IV contrast if no allergy and adequate renal function) and radionuclide bone scan. MRI abdomen/pelvis is an acceptable alternative.
f. For every 3 week dosing schedules, docetaxel will be administered on Day 1 of every 21-day cycle, with concomitant prednisone 5 mg BID. For weekly dosing schedule, docetaxel will be administered on Days 1 and 8 of every 21-day cycle. Treatment will be administered for up to 9 cycles. If there is no evidence of clinical or radiographic progression, patients will discontinue docetaxel and taper prednisone over a period of 21 days. Patients with stable disease or better as best response will have the option of

discontinuing docetaxel after 6 cycles of protocol therapy. The dose schedule of maintenance ribociclib monotherapy will be the dose used immediately preceding discontinuation of docetaxel, given on days 1-14 of every 21-day cycle.
g. Neupogen will be administered subcutaneously daily on days 15-18 of every cycle. Dose will be determined by actual body weight (300 mcg if < 70 kg on C1D1; 480 mcg if ≥ 70 kg). Alternative dosing schedules of neupogen may be utilized depending on dosing schedule of study therapy (see Section 6).

Phase 2 Schedule (N = 29 evaluable patients)

Study Assessments	Screen[a]	Cycle 1			Cycle 2 and Every Cycle Thereafter	End of Study (within 30 days of last treatment)
		D 1	D8	D15	Day 1	
Informed Consent	X					
Medical History	X					
Physical Examination	X	X	X	X	X	X
Concurrent Medications	X	X	X	X	X	X
ECOG/KPS Performance Status	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Weight and Height	X	X			X	X
CBC + Differential[b]	X	X	X	X	X	X
PT/PTT + chemistry panel[b]	X	X			X	X
Serum PSA	X	X			X	X
Serum testosterone	X					
MUGA or echocardiogram	X					
12-lead ECG[c]	X			X	X	
CTC and Cell-Free ctDNA collection[d]	X					
Plasma/serum/PBMC banking[e]	X				X	X
Tumor Biopsy[f]	X					
Gallium citrate PET[g]	X				X	
Tumor Assessment[h]	X				X	X
Docetaxel Administration[i]		X			X	
Neupogen Administration[j]		See Section 6 for schedule				
Ribociclib Administration[k]		Dosed Daily (see Section 6 for schedule)				

a. Screening labs may be used on Cycle 1 Day 1 if drawn within 3 days prior to start of treatment.
b. For every 3-week docetaxel dosing schedule, CBC + differential will be measured Days 1, 8, and 15 of Cycle 1, Days 1, 8 (+/- 2 days), and 15 (+/- 2 days) during Cycles 2-3, and then on Day 1 of Cycle 4 and every cycle thereafter. For weekly docetaxel dosing schedule, CBC + differential will be measured on Days 1, 8, and 15 of Cycle 1, Days 1, 8, and 15 (+/- 2 days) during Cycles 2-3, and then Days 1 and 8 of every cycle thereafter. Chemistry panel as described in **Section 5.1.2**
c. 12-lead ECG will be performed during Screening, Cycle 1 Day 15, and on Day 1 of every cycle thereafter.
d. See Section 5.4 and 5.5 and **Appendix 6** regarding collection instructions
e. Plasma/serum/PBMC banking is optional. Peripheral blood mononuclear cells (PBMCs) will be collected and banked at baseline. Serum/plasma will be banked at baseline, every 3 months (+/- 4 weeks) from Cycle 1 Day 1 until treatment discontinuation, and at the time of disease progression.
f. Optional tumor biopsy to be performed in patients with accessible lesion. Biopsy to be performed at Screening following completion of Screening scans including gallium citrate PET. Results of pathologic analysis do not need to be available prior to initiation of protocol therapy provided there is prior pathologic confirmation of prostate cancer. See Section 5.6 and **Appendix 7** for collection/processing information.
g. Optional Gallium-68 citrate PET scan to be completed at Screening and on Cycle 2 Day 1 of protocol therapy (+/- 7 days) (UCSF patients only). See Section 5.7 for details regarding the scan/procedure.

h. Tumor assessment will be completed at the completion of every 3 treatment cycles (9 weeks). Tumor assessment to include CT chest/abdomen/pelvis (with IV contrast if no allergy and adequate renal function) and radionuclide bone scan. MRI abdomen/pelvis is an acceptable alternative.
i. For every 3 week dosing schedules, docetaxel will be administered on Day 1 of every 21-day cycle, with concomitant prednisone 5 mg BID. For weekly dosing schedule, docetaxel will be administered on Days 1 and 8 of every 21-day cycle. Treatment will be administered for up to 9 cycles. If there is no evidence of clinical or radiographic progression, patients will discontinue docetaxel and taper prednisone over a period of 21 days. Patients with stable disease or better as best response will have the option of discontinuing docetaxel after 6 cycles of protocol therapy. The dose schedule of maintenance ribociclib monotherapy will be the dose used immediately preceding discontinuation of docetaxel, given on Days 1-14 of every 21-day cycle.
j. Neupogen will be administered subcutaneously daily on days 15-18 of every cycle. Dose will be determined by actual body weight (300 mcg if < 70 kg on C1D1; 480 mcg if ≥ 70 kg). Alternative dosing schedules of neupogen may be utilized depending on the recommended phase 2 dosing schedule of study therapy (see Section 6.2).
k. Ribociclib daily dose and schedule to be determined from Phase 1 portion of study.

5.3 Plasma/Serum/Peripheral Blood Mononuclear Cell (PBMC) Banking

Blood will be collected at specified time points for Plasma, Serum, and PBMC banking. The UCSF-HDFCCC Tissue Bank will serve as a repository for banking human samples. Specimen and data registries will be kept by the UCSF-HDFCCC. This registry will have a coordinated database to protect patient confidentiality and safety. The samples will receive a patient- insensitive identifier and the link to patient identity will be kept in a locked file with access only by the director of the Tissue Bank. Other investigators will have access to the samples only through established Tissue Core procedures. That is, investigators must submit a written request to use the stored samples as part of an IRB-approved protocol that is reviewed by the Tissue Core committee. This review limits the testing that can be done on these samples. No information about germ-line genetic mutations will be done on these samples. The collection of these specimens is optional and patients have the right at any time to request that all remaining samples be destroyed. The patient or relatives may be contacted about future, additional research on stored samples, if necessary. Additional written consent will be required if additional samples are to be taken. Please see **Appendix 5** for additional details.

5.4 Cell-Free Circulating Tumor DNA

A next generation DNA sequencing platform will be utilized in the current study. The platform is fully CLIA-certified and assesses many of the most common driver mutations encountered across solid tumor malignancies, including complete exon and partial intron coverage of, RB1, MYC, AR, and PTEN, CDK4, CDK6, CCND1, CCND2, among others. In addition, copy number determination of MYC, CDK4, and CDK6 will be determined. For the specimen collection, 10 mL of whole blood will be collected using the supplied research kit with blood collection tubes at Screening. Samples will be shipped to Guardant Health. Please see **Appendix 6** for collection and shipping instructions.

5.5 Circulating Tumor Cells

CTC enumeration will be performed via the Epic Sciences platform. The Epic Sciences platform is a novel CTC detection technology that uses unselected enumeration and characterization of multiple different CTC types including “traditional” CTCs (CK+, CD45-, and morphologically distinct from surrounding white blood cells, similar to the Veridex definition), EMT candidates (CK-, CD45-, and morphologically distinct from surrounding white blood cells), and small cell CTCs (CK+, CD45-, and morphologically similar to white blood cells). The technology was developed with a view to providing a fluid biopsy with features, specifications and performance criteria similar to current pathology practice. The platform allows multiplexed analysis of different protein biomarkers from the

same blood sample, fluorescence in-situ hybridization (FISH) analysis of relevant genes, and individual cell capture for detailed molecular interrogation. The platform has demonstrated molecular characterization concordance in a blinded CRPC patient study between concurrently obtained biopsies of bone metastases and Epic-captured CTCs. In the study, 80% (12 of 15) of tumors with PTEN loss in the bone biopsy also harbored PTEN loss in Epic CTCs, demonstrating a strong genomic concordance and the ability to measure intra-patient genomic heterogeneity. Please see **Appendix 6** for collection and processing details.

5.6 Tumor biopsy (Optional, if accessible lesion is present)

Optional image-guided biopsies will be performed prior to start of protocol therapy. Lesions will be chosen based upon the strength of the evidence suggesting the presence of metastasis and with the goal of minimizing patient risk. Soft tissue lesions and lesions with documented radiologic progression should be prioritized for biopsy. If the Radiologist in charge of the procedure cannot identify a lesion amenable for biopsy, the patient will still be eligible for study participation.

Biopsies will be performed in an interventional radiology suite with radiological guidance (typically CT or MRI) in accordance with the standard operating procedure in **Appendix 7** and institutional standards. CT or MRI will confirm designated lesions immediately prior to biopsy. Once the target lesion(s) is identified, up to six (6) cores will be obtained. Preferably, a 16-gauge Bonopty™ needle or biopsy needle with an equivalent 16-gauge bore will be used to biopsy the metastatic lesion. If the lesion is a bone metastasis, the Bonopty needle will be passed through the cortical bone and into the target lesion. Optimal results are obtained when the biopsies are performed on medullary bone directly adjacent to a blastic lesion. Soft tissue biopsies should be performed to ensure a core of approximately 10 to 20 mm in length is obtained. Extracted cores will be immediately frozen on a pre-frozen bed of OCT (Optimal Cutting Temperature compound used for frozen sections), covered with additional OCT, and stored at -80° C until shipment (see **Appendix 7**). All biopsy specimens will be delivered to the Feng laboratory at UCSF.

Frozen biopsies will be processed for RNA analysis using laser capture microdissection (LCM) and RNA amplification using adaptations of previously published methods [36]. Briefly, 8-micron frozen sections are obtained from each biopsy specimen and stained with H&E. Sections will be loaded into the Aperio Digital Imaging system. Multiple sequential 8-micron biopsies are performed prior to rapid H&E staining and dehydration with sequential immersion in xylene. The air-dried slides are put into a LCM system and prostate cancer cells are identified and collected. Cell material selected for analysis is dissolved in RNA or DNA isolation buffer and RNA and DNA are isolated separately using standard commercially available kits. RNA and DNA are quantified using the RiboGreen or PicoGreen kits (Invitrogen, Inc) and RNA quality is assessed with an Agilent 2100 Bioanalyzer using the RNA 6000 Pico Kit (Agilent, Inc). Similarly, DNA is collected from separate but adjacent frozen sections and isolated. DNA is quantified using PicoGreen quantification.

Gene copy number changes will be performed using a CGH methodology as described above in Section 5.5. RNA sequencing methodology will be used to determine levels of gene expression. LCM collected material will be lysed with 5 microliters of Prelude Lysis Buffer (NuGen, San Carlos, CA); subjected to cDNA synthesis and amplification without transfer (NuGen, Ovation RNA-seq with some modifications to standard protocol); selected for size and processed using the mixed cDNA standard library preparation performed using TruSeq protocol (Illumina, San Diego, CA). Paired-end sequencing will be performed on the Illumina HiSeq 2000.

5.7 Gallium-68 Citrate PET Scan (Optional, For UCSF Patients Only)

Ga-68 citrate is a radiopharmaceutical that will be produced under cGMP under the direction of [redacted] the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility, The radiopharmaceutical will be prepared in the same facility in which the injection and imaging will take place, the China Basin Imaging Center. Ga-68 citrate will be administered on an outpatient basis. It will be administered a single time intravenously prior to PET imaging. The one-time nominal injected dose will be up to 20 mCi Ga-68.

Patient shall begin imaging within 6 hours following injection of the radiopharmaceutical. Coverage for the scan will extend from the patient's vertex through the toes. The entire imaging study will take roughly 60 minutes.

No formal report of the findings from imaging studies will be created. Each study will be reviewed by a board certified nuclear medicine physician and radiologist within two working days of the completion of the study. If any unexpected findings are visualized, these will be reported to the treating health care provider, who will then contact the patient if additional work-up needs to be performed.

6 TREATMENT PLAN

6.1 Dose and schedule

1. Each cycle is 21 days long. A ± 3 day window is allowable for administration of chemotherapy for scheduling purposes for cycle 2 and beyond.

2. Two separate dose guidelines will be used in this trial:
   a. Cohort dose level (referred to by Roman numerals: I, II, III, etc).
   b. Individual patient dose level: individual patients may have their doses modified (reduced) for toxicity (referred to by Arabic numerals: 0, -1, -2).

   There are approximately 3 planned dose cohorts in the Phase 1 portion of the study. Approximately 9 to 18 patients will be treated on the Phase 1 portion of the study.

3. The starting cohort dose level for docetaxel will be 75 mg/m^2, administered on day 1 of each cycle. Prednisone will be fixed at 5 mg PO BID. The starting dose level and schedule for ribociclib will be 200 mg orally once daily, starting on day 1 of the 21-day cycle.

4. If dose level I is not tolerated, then alternative dosing schedules of docetaxel will be evaluated, starting with dose level IA.

5. Depending on the safety data observed, alternative dosing schedules and intermediate dose levels of ribociclib may be investigated as outlined in Table below (Cohort Dose Levels IC – IIIC).

Cohort Dose Levels (3+3 Design)

		Patient number	**Docetaxel (day 1 of 21-day cycle)**	**Ribociclib Daily**	**Prednisone**	**Filgrastim***
Dose Level	I**	3+3	75 mg/m^2	200 mg/day	5 mg PO BID	SubQ daily days 15-18
	II	3+3	75 mg/m^2	400 mg/day	5 mg PO BID	SubQ daily days 15-18
	III	3+3	75 mg/m^2	600 mg/day	5 mg PO BID	SubQ daily days 15-18

Alternate Dosing Schema with Docetaxel 60 mg/m^2 (3+3 Design)

Dose Level		Patient number	**Docetaxel (day 1 of 21-day cycle)**	**Ribociclib Daily**	**Prednisone**	**Filgrastim***
	IA	3+3	60 mg/m^2	200 mg/day	5 mg PO BID	SubQ daily days 15-18
	IIA	3+3	60 mg/m^2	400 mg/day	5 mg PO BID	SubQ daily days 15-18
	IIIA	3+3	60 mg/m^2	600 mg/day	5 mg PO BID	SubQ daily days 15-18

Alternate Dosing Schema with Weekly Docetaxel (3+3 Design)

Dose Level		Patient number	**Docetaxel (days 1, 8 of 21-day cycle)**	**Ribociclib Daily**	**Prednisone**	**Filgrastim***
	IB	3+3	30 mg/m^2	200 mg/day	5 mg PO BID	SubQ daily days 15-18
	IIB	3+3	30 mg/m^2	400 mg/day	5 mg PO BID	SubQ daily days 15-18
	IIIB	3+3	30 mg/m^2	600 mg/day	5 mg PO BID	SubQ daily days 15-18

* Filgrastim will be administered subcutaneously daily on days 15-18 of every cycle. Dose will be determined by actual body weight (300 mcg if < 70 kg on C1D1; 480 mcg if ≥ 70 kg). Filgrastim may also be administered as clinically necessary per investigator discretion for grade 3 or higher neutropenia. It should not be administered within 24 hours prior to or after docetaxel infusion.
**If dose level I is determined to have exceeded the MTD alternative dosing schedules of docetaxel will be evaluated, as indicated above, starting with dose level IA. Dose escalation will then proceed from level IA to level IIIA as tolerated. If dose level IA, IIA, or IIIA is not tolerated, weekly docetaxel dosing may be explored starting with the corresponding dose level (e.g. IA → IB, IIA → IIB, IIIA → IIIB).

Alternative Ribociclib Dosing Schedule (3+3 Design)

Dose Level		Patient number	**Docetaxel (day 1 of 21- day cycle)**	**Ribociclib Daily^**	**Prednisone**	**Filgrastim***
	IC	3+3	60 mg/m^2	200 mg/day	5 mg PO BID	SubQ daily days 5-7
	IIC	3+3	60 mg/m^2	300 mg/day	5 mg PO BID	SubQ daily days 5-7

	IIIC	3+3	60 mg/m^2	400 mg/day	5 mg PO BID	SubQ daily days 5-7

* Filgrastim will be administered subcutaneously daily on days 5-7 of every cycle. Dose will be determined by actual body weight (300 mcg if < 70 kg on C1D1; 480 mcg if ≥ 70 kg). Additional doses of filgrastim will also be administered as clinically necessary for grade 3 or higher neutropenia. It should not be administered within 24 hours prior to or after docetaxel infusion.

^ Ribociclib will be dosed daily on days 1-4, 8-15 of every 21-day treatment cycle.

6. The prednisone dose will be 5 mg by mouth twice a day, continuously. At the conclusion of docetaxel treatment, prednisone will be tapered over two weeks or longer at the discretion of the treating provider.

7. When calculating body surface areas, actual heights and weights should be used. There should be no adjustment to "ideal" weight. The total dose delivered should be rounded to the nearest mg. The dose should be adjusted during each cycle for the patient's current weight. If there has been an increase in weight of 5% or greater that the investigator suspects is secondary to edema, the investigator may use discretion to utilize the weight from the prior cycle to calculate chemotherapy dosage.

8. Patients who do not receive at least 50% of ribociclib doses during cycle 1 for reasons other than toxicity will be considered inevaluable and will be replaced.

6.1.1 Dose escalation and de-escalation rules

Ribociclib will be escalated according to the rules outlined below:

1. The dose-limiting toxicity window will be the first 21-day treatment cycle.

2. If 0 of 3 patients in a cohort experience dose limiting toxicities, then the next cohort of 3 patients will be treated at the next higher dose level.

3. If 1 of 3 patients in a cohort experiences a DLT then the cohort will be expanded to treat an additional three patients. If only one of 6 patients experiences a DLT, then the next cohort of patients will be treated at the next higher dose level.

4. If two or more patients in a cohort experience a DLT, then the MTD has been exceeded. The previous dose level will be considered the MTD.

5. If more than 1 of 6 patients experience a DLT at dose level IA then the study will be terminated, as the MTD cannot be determined and de-escalation from dose level IA is not planned.

6. Per Investigator discretion the recommended phase 2 dose/schedule of ribociclib and docetaxel may be established (see Section 6.2 below) in the absence of reaching MTD, based on the cumulative safety data of the treatment regimen.

6.1.2 Supportive care guidelines

1. Patients may receive full supportive care including, transfusions of blood products, growth factors, bone-modifying agents, antibiotics, and anti-emetics.

2. A list of prohibited medications and medications to be used with caution is found in **Appendices 2 and 3** respectively.

3. Radiation therapy may not be administered concurrently with protocol therapy. If the patient requires the need for radiation therapy during the course of protocol therapy this will be considered evidence of clinical progression and the patient will be removed from study.

4. Filgrastim should not be administered within 24 hours of docetaxel infusion. Ribociclib should be held for grade 3 or higher neutropenia (see Section 6.3).

5. All patients will be premedicated to prevent a hypersensitivity reaction related to docetaxel with intravenous or oral dexamethasone or equivalent dose of alternative steroid.

6.2 Phase 2 Dosing Schedule

The recommended phase 2 dose and schedule of ribociclib in combination with docetaxel will be either equivalent to or lower than the MTD (or maximally administered cumulative dose if MTD not reached) of the Phase 1 portion of the study. Dose modifications for individual patients in the event of toxicity will be similar for Phase 1b and Phase 2, and will follow guidelines outlined below in Section 6.3.2.

6.3 Toxicity Management and Dose Modifications

6.3.1 Dose limiting toxicity definitions

A dose-limiting toxicity (DLT) will be defined as a treatment-regimen related toxicity as follows:

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 3 thrombocytopenia with significant hemorrhage
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 or 4 febrile neutropenia
ECG QT interval	QTc interval ≥ 501 ms on at least 2 separate ECGs
Cardiac	Cardiac toxicity ≥ CTCAE grade 3 Clinical signs of cardiac disease, such as unstable angina or myocardial infarction,
Gastro-intestinal	≥ CTCAE grade 3 vomiting ≥ 48 hours despite optimal anti-emetic therapy ≥ CTCAE grade 3 diarrhea ≥ 48 hours despite optimal anti-diarrhea treatment
Hepato-biliary	≥ CTCAE grade 3 total bilirubin ≥ CTCAE grade 2 ALT with a ≥ grade 2 bilirubin elevation of any duration in the absence of liver metastases ≥ CTCAE grade 3 ALT for >4 consecutive days CTCAE grade 4 ALT or AST Grade 4 serum alkaline phosphatase >7 consecutive days
Any category	Any toxicity that results in delivery of less than 66 % of the expected cumulative dose of ribociclib during Cycle 1
Non-hematologic events	≥ CTCAE grade 3 non-hematological toxicity that delays administration of either study drug for more than 2 weeks ≥ CTCAE grade 3-4 non-hematologic laboratory abnormalities
Exceptions to DLT criteria	Grade 3 alopecia
	< 5 days of CTCAE grade 3 fatigue
	Grade 3 fever or infection without neutropenia < 5 days duration
	Adverse events solely related to prednisone or androgen deprivation therapy in the judgment of Study Investigator.
	Grade 3 hypersensitivity infusion reaction to docetaxel
	Grade 3-4 increase in indirect bilirubin indicative of M. Meulengracht/Gilbert's syndrome
	Grade 3 increase in serum lipase and/or amylase for < 7 consecutive days without clinical signs or symptoms of pancreatitis
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by investigator to be clinically insignificant
CTCAE version 4.03 should be used for grading. Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines.	

6.3.2 Guidelines for individual patient dose modifications for toxicity (Phase 1b and Phase 2)

6.3.2.1 General Dose Modification Guidelines

1. Individual patient dose reduction for toxicity during the DLT window (cycle 1) in the Phase 1b portion of the study only will not be permitted except for toxicity meeting criteria for dose-limiting toxicity (Section 6.3.1).
2. Permanently discontinue protocol therapy for related Grade 4 non-hematologic adverse events of any duration except for:
    a. Clinically insignificant laboratory abnormalities that resolve with optimal treatment within 48 hours
    b. Vomiting and diarrhea that resolve within 48 hours with optimal treatment
3. Hold treatments for related Grade 3 adverse events with subsequent dose-reduction, if such adverse events return to Grade ≤ 1 or baseline within two weeks, treatment can be continued at one lower dose level as outlined in Section 6.3.2.7
4. Dose reduction/discontinuation of ribociclib should occur before or concurrently with docetaxel for overlapping toxicities

The following sections are recommended dose interruption/reduction guidelines. Investigator-discretion and clinical judgment are to be utilized in deciding whether to interrupt and/or reduce dose even if not required per protocol.

The schema for dose modification for toxicity for individual patients are as follows:

For patients treated with every 3-week docetaxel at 75 mg/m^2 and a starting ribociclib dose of **600 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	75 mg/m^2	600 mg
-1	75 mg/m^2	400 mg
-2	75 mg/m^2	200 mg
-3	60 mg/m^2	200 mg

For patients treated with every 3-week docetaxel at 75 mg/m^2 and starting ribociclib dose of **400 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	75 mg/m^2	400 mg
-1	75 mg/m^2	200 mg
-2	60 mg/m^2	200 mg

For patients treated with every 3-week docetaxel at 75 mg/m^2 and starting ribociclib dose of **200 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	75 mg/m	200 mg
-1	60 mg/m^2	200 mg

For patients treated with every 3-week docetaxel at 60 mg/m^2 and a starting ribociclib dose of **600 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	60 mg/m^2	600 mg
-1	60 mg/m^2	400 mg
-2	60 mg/m^2	200 mg
-3	50 mg/m^2	200 mg

For patients treated with every 3-week docetaxel at 60 mg/m^2 and starting ribociclib dose of **400 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	60 mg/m^2	400 mg
-1	60 mg/m^2	300 mg
-2	60 mg/m^2	200 mg
-3	50 mg/m^2	200 mg

For patients treated with every 3-week docetaxel at 60 mg/m^2 and starting ribociclib dose of **300 mg/day:**

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	60 mg/m^2	300 mg
-1	60 mg/m^2	200 mg
-2	50 mg/m^2	200 mg

For patients treated with every 3-week docetaxel at 60 mg/m^2 and starting ribociclib dose of **200 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	60 mg/m^2	200 mg
-1	50 mg/m^2	200 mg

For patients treated with weekly docetaxel and a starting ribociclib dose of **600 mg/day**:

Dose Level	Weekly Docetaxel Dose	Ribociclib Daily Dose
1	30 mg/m^2	600 mg
-1	30 mg/m^2	400 mg
-2	30 mg/m^2	200 mg
-3	25 mg/m^2	200 mg

For patients treated with weekly docetaxel at 30 mg/m^2 and starting ribociclib dose of **400 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	30 mg/m^2	400 mg
-1	30 mg/m^2	200 mg
-2	25 mg/m^2	200 mg

For patients treated with weekly docetaxel at 30 mg/m^2 and starting ribociclib dose of **200 mg/day**:

Dose Level	Every 3-Week Docetaxel Dose	Ribociclib Daily Dose
1	30 mg/m^2	200 mg
-1	25 mg/m^2	200 mg

5. <u>The patient will be removed from protocol therapy for unacceptable toxicity if:</u>

a. There is a delay of treatment > 21 days for recovery from toxicity to permissible level

OR

b. Patients require dose reduction below 200 mg/day of ribociclib plus 50 mg/m^2 of every 3-week docetaxel (or below ribociclib 200 mg/day plus 25 mg/m^2 weekly docetaxel) for treatment regimen-related toxicity.

Note that patients removed from protocol therapy for toxicity will be followed on study until the time of progression or initiation of non-protocol therapy.

6. Dose modifications are made according to the system showing the greatest degree of toxicity.

7. Once a dose has been reduced for toxicity, it will not be re-escalated for an individual patient.

6.3.2.2 Treatment of hypersensitivity reactions to docetaxel

In case of hypersensitivity reactions, the investigator should institute treatment measures deemed medically appropriate per institutional guidelines. Based on prior experience with paclitaxel, the following treatment recommendations may be applicable. Investigator discretion should be taken regarding any additional measures to be instituted.

CTCAE Grade 1 Allergic Reaction/Hypersensitivity (transient rash, drug fever < 38°C):

- Supervise at the bedside without further treatment. Consider decreasing rate of infusion until recovery from symptoms.

CTCAE Grade 2 Allergic Reaction/Hypersensitivity (urticaria, drug fever ≥ 38°C):

- Interrupt the infusion of docetaxel.
- After recovery of symptoms, resume the infusion at a slower rate and if no further symptoms appear, complete the administration of the dose. If symptoms recur, discontinue infusion and follow guidelines below.

Recurrent CTCAE Grade 2 or CTCAE Grade 3 or 4 Allergic/Hypersensitivity Reactions:

- Stop the infusion.
- Administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids (see discussion below) and consider epinephrine and bronchodilators as clinically indicated.
- For recurrent grade 2 or grade 3 reactions, prior to rechallenge and with all subsequent cycles, consider both an H1 and H2 blocker intravenously plus dexamethasone 20 mg x 2 doses (orally or intravenously) 12 and 6 hours pre docetaxel. Grade 4 reactions are considered severe hypersensitivity reactions, and rechallenge is contraindicated.

6.3.2.3 Dose Modifications for Hematologic Toxicity

Toxicity	Grade	Dose Adjustment for Docetaxel	Dose Adjustment for Ribociclib
Thrombocytopenia	1 ≥75 x 10^9/L	No dose adjustment required.	No dose adjustment required.
	2 50 x 10^9/L - <75 x 10^9/L	Day 1: Hold docetaxel until count is > 75 x 10^9/L, then restart protocol therapy at same dose level. Mid-cycle: No dose adjustment required.	Dose interruption until recovery to grade ≤1. Re-initiate protocol therapy at the same dose level.
	3 (without clinically significant bleeding) 25 x 10^9/L - <50 x 10^9/L	Day 1: Hold docetaxel until count is > 75 x 10^9/L, then restart protocl therapy at one lower	Dose interruption until recovery to grade ≤1. Re-initiate protocol therapy at the same

		dose level. If second dose reduction is required patient will be removed from protocol therapy. Mid-cycle: No dose adjustment required	dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and re-initiate protocol therapy at the next lower dose level.
	Grade 3 with clinically significant bleeding	Day 1: Hold docetaxel until count > 75 x 10^9/L and bleeding resolved, then restart protocol therapy at one lower dose level. Mid-cycle: Hold next docetaxel dose until count > 75 x 10^9/L and bleeding resolved, then restart protocol therapy at one lower dose level. If toxicity recurs (grade 3 thrombocytopenia with clinically significant bleeding), discontinue protocol therapy.	Dose interruption until recovery to grade ≤1. Re-initiate protocol therapy at the next lower dose level. If toxicity recurs (grade 3 thrombocytopenia with clinically significant bleeding), discontinue protocol therapy.
	4 <25 x 10^9/L with or without bleeding.	Day 1: Hold docetaxel until count > 75 x 10^9/L and bleeding resolved, then restart protocol therapy at one lower dose level. Mid-cycle: Hold next docetaxel dose until count > 75 x 10^9/L and bleeding resolved, then administer protocol therapy at one lower dose level. If a second dose reduction is required for docetaxel, patient will be removed from study therapy.	Dose interruption until recovery to grade ≤1. Re-initiate protocol therapy at the next lower dose level. • If toxicity recurs at grade 4: discontinue protocol therapy.
Absolute neutrophil count (ANC)	1 ≥1.5 x 10^9/L	No dose adjustment required.	No dose adjustment required.
	2 1.0 - <1.5 x 10^9/L	Day 1: Hold docetaxel until ANC > 1.5 x 10^9/L, then restart protocol therapy at same dose level. Mid-cycle: No dose adjustment required.	No dose adjustment required.
	3 0.5 - <1.0 x 10^9/L	Day 1: Hold docetaxel until ANC > 1.5 x 10^9/L, then restart protocol therapy at same dose level. Mid-cycle: No dose adjustment required.	Dose interruption until recovery to >1.0 x 10^9/L. Re-initiate protocol therapy at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to >1.0 x 10^9/L • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then re-initate protocol therapy at the next lower

			dose level. Filgrastim as clinically indicated.
	4 <0.5 x 10^9/L	Day 1: Hold docetaxel until ANC > 1.5 x 10^9/L, then restart treatment at the same dose level. If toxicity recurs at grade 4 on day 1 of subsequent treatment cycle, hold docetaxel until ANC > 1.5 x 10^9/L, then restart at one lower dose level. Mid-cycle: No dose adjustment required.	Dose interruption until recovery to >1.0 x 10^9/L. Re-initiate protocol therapy at the same dose level. • If toxicity recurs at grade 4: temporary dose interruption until recovery to >1.0 x 10^9/L and re-initiate protocol therapy at the next lower dose level. Filgrastim as clinically indicated.
Febrile neutropenia	Grade 3 or 4	Hold docetaxel until ANC > 1.5 x 10^9/L and no fever, then restart protocol therapy at one lower dose level. For recurrent grade 3 or 4 febrile neutropenia, discontinue protocol therapy.	Dose interruption until improvement of ANC ≥ 1.1 x 10^9/L and no fever. Restart protocol therapy at the next lower dose level. • If febrile neutropenia recurs, discontinue protocol therapy.
Anemia (Hemoglobin)	1 > 10 g/dL	No dose adjustment required.	No dose adjustment required.
	2 8.0 – 10.0 g/dL	No dose adjustment required.	No dose adjustment required.
	3 <8.0 g/dL	No dose adjustment required; transfuse as indicated.	Dose interruption until recovery to grade ≤ 2; re-initiate ribociclib at the same dose level. Transfuse as indicated.
	4 Life-threatening consequences; urgent intervention indicated	Discontinue protocol therapy.	Discontinue protocol therapy.

6.3.2.4 Dose Modifications for Hepatic Toxicity

Patients who develop abnormal liver function tests as defined below, for any reason while on study, will have treatment held and/or reduced according to the following schedules:

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN)	Maintain ribociclib level with LFTs monitored bi-weekly Hold docetaxel until total bilirubin improves to grade 0, then resume at one lower dose level.

Grade 2 (> 1.5 – 3.0 x ULN)	Interrupt dosing of ribociclib. If resolved to ≤ grade 1 in ≤ 21 days, then maintain current dose level. If resolved to ≤ grade 1 in > 21 days or toxicity recurs, then reduce 1 dose level. If toxicity recurs after two dose reductions, discontinue ribociclib. Hold docetaxel until total bilirubin improves to grade 0, then resume at one lower dose level.
Grade 3 (> 3.0 – 10.0 x ULN)	Interrupt dosing of ribociclib. If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of ribociclib. If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue ribociclib Hold docetaxel until total bilirubin improves to grade 0, then resume at one lower dose level. If toxicity recurs, discontinue docetaxel.
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib and docetaxel.
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	

AST or ALT	
AST or ALT without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1.
Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN) or from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN)	Interrupt dosing of ribociclib. If resolved to ≤ baseline value in ≤ 21 days, then maintain dose level. If resolved to ≤ baseline value in > 21 days or toxicity recurs, then reduce 1 dose level. If toxicity recurs after two dose reductions or recovery to ≤ baseline value is > 28 days, discontinue ribociclib. Hold docetaxel until AST or ALT < grade 3, then resume at one lower dose level.
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Interrupt dosing of ribociclib until resolved to ≤ baseline value, then lower 1 dose level of ribociclib. If recovery to ≤ baseline value is > 28 days, discontinue ribociclib. If toxicity recurs, discontinue ribociclib. Hold docetaxel until AST or ALT < grade 3, then resume at one lower dose level.
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib and docetaxel.

AST or ALT and concurrent Bilirubin elevation	
AST or ALT ≥ grade 2 (> 3 x ULN) in patients with normal values at baseline and total bilirubin > 2 x ULN or AST or ALT ≥ grade 3 (> 5 x ULN) in patients with grade 1 or 2 at baseline, and total bilirubin > 2 x ULN	Discontinue ribociclib. Hold docetaxel until AST or ALT < grade 3 and total bilirubin grade 0, then resume at one lower dose level. If toxicity recurs, discontinue docetaxel.
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

Additional follow-up for hepatic toxicities
Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), alkaline phosphatase, and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.

6.3.2.5 Cardiovascular

Dose modification of ribociclib in case of QT prolongation will be as follows:

Grade	Dose Modification
For all grades	1. Check the quality of the ECG. 2. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt ribociclib administration, correct with

	supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib.
1 QTc 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
2 QTc 481-500 ms	Interrupt ribociclib. Perform steps 1-4 as directed "For All Grades." Perform a repeat ECG one hour after the first QTcF of ≥418ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, Restart ribociclib with dose reduced by 1 dose level. Refer to Section 6.3.2.1 for dosing schedule. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms
3 QTc ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." • Consider consulting a local central cardiologist to perform a repeat ECG one hour after the first QTcF of > 501 ms. • If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, ribociclib should be reduced by 1 dose level. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. **Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF > 501 ms** • If QTcF of ≥ 501 ms recurs, discontinue ribociclib
4 QT/QTc ≥ 501 **or** > 60 ms change from baseline **and** Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." • Obtain local cardiologist consultation • Perform a repeat ECG one hour after the first QTcF of ≥501 ms • If QTcF remains ≥501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF

6.3.2.6 Hypersensitivity infusion reaction.

No dose reductions should be made. Acute hypersensitivity reactions related to docetaxel infusion should be managed according to Section 6.3.2.2.

6.3.2.7 All other adverse reactions

For treatment regimen-related toxicities ≥ grade 3 (excluding the hematologic, liver, and cardiac toxicities outlined above, as well as grade 3 nausea/vomiting/diarrhea/fatigue lasting less than 48 hours with optimal medical management, any grade alopecia, or non-clinically significant laboratory abnormalities that resolve within 48 hours with optimal medical management), both drugs should be withheld until resolution to ≤ grade 1 (or to baseline if baseline was greater than grade 1). Treatment may be restarted at next lower dose level if the toxicity improves to grade 1 or lower within 2 weeks of onset of adverse event. If toxicity recurs at grade 3 or higher, patients will be required to discontinue study therapy.

Ribociclib should be held for grade 2 related toxicities and restarted at the original dose level once recovered to grade ≤ 1. If the same toxicity recurs at grade 2, interrupt ribociclib until recovery to grade ≤ 1, then restart ribociclib at the next lower dose level.

Toxicities solely related to corticosteroid use (hyperglycemia, insomnia, hypertension, etc.) and androgen deprivation therapy (hot flashes, gynecomastia, erectile dysfunction, etc.) will not require mandatory dose reduction. **Treating physicians may modify the doses of prednisone as clinically indicated.** Cessation of prednisone therapy is not a reason to remove a patient from protocol therapy or to be considered a DLT.

6.4 Cycle Delays

Initiation of subsequent cycles may be delayed for a maximum of three weeks for toxicity or at the discretion of the treating physician. Any patient who fails to recover from a treatment related toxicity to baseline or Grade 1 within 21 days of scheduled retreatment will be removed from the study and followed for progression or initiation of non-protocol therapy.

6.5 Duration of Therapy

In the absence of treatment delays due to toxicity(ies), treatment may continue until one of the following criteria applies:

- Disease progression (see Section 8)
- Unacceptable toxicity according to above definition (Section 6.3.2.1)
- Patient withdrawal from study
- Study closure

When a patient is discontinued from the study, the reason(s) for discontinuation should be documented. Follow-up should be maintained every three months until progression or initiation of non-protocol therapy. Patients who experienced any drug-related toxic effects will be followed at least every four weeks until all study drug-related toxicities resolve, stabilize, return to baseline, or are deemed irreversible.

7 DRUG INFORMATION *(adapted from the Investigators Brochure and package insert)*

7.1 Docetaxel

Classification and Mode of Action

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Preparation and Administration:

TAXOTERE Injection Concentrate (20 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw TAXOTERE from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. TAXOTERE vials should be stored between 2 and 25° C (36 and 77° F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate vials to stand at room temperature for approximately 5 minutes before use.
2. Using only a 21 gauge needle, aseptically withdraw the required amount of TAXOTERE injection concentrate (20 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
3. Thoroughly mix the infusion by gentle manual rotation.
4. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.
5. TAXOTERE infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

The TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25° C) and lighting conditions.

How Supplied

Docetaxel will be obtained via manufacturer via commercial insurance.

Potential Drug Interactions

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients

receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided [see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)].

7.2 Ribociclib

Classification and Mode of Action:

Ribociclib inhibits the CDK4/CCND1 and CDK6/cyclin-D3 enzyme comples (IC_{50} values of 0.01 and 0.039 micromolar concentration respectively).

Nomenclature: 7-Cyclopentyl-N,N-dimethyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}-7H-pyrrolo[2,3-d] pyrimidine-6-carboxamide succinate (1:1)

Molecular formula
$C_{23}H_{30}N_8O.C_4H_6O_4$

Relative molecular mass
Free base: 434.54
Salt form: 552.63

Physical state
Light tan to yellow powder

How Supplied

The ribociclib drug product is planned for oral administration. The available clinical forms are hard gelatin capsules (50 mg and 200 mg), and film-coated tablets (200 mg)

The shelf life of the drug product is established based on ongoing stability studies and may be extended during the clinical study. The film-coated tablets are stored in HDPE bottles with induction seals and child resistant polypropylene caps.

Ribociclib is a potent investigational new drug that has not been fully evaluated. Exercise appropriate hygiene and clinical practice precautions.

Availability

Ribociclib will be supplied by Novartis or its designee as 50 mg or 200 mg film-coated tablets.

Packaging and labeling

Study Treatment	Packaging	Labeling
Ribociclib (ribociclib)	Film-coated tablets in bottles	Labeled as 'Ribociclib' or 'LEE011'

Drug Supply and Storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

Supply and storage of study treatment

Study Treatment	Supply	Storage
Ribociclib	Bulk supplied by Novartis	Refer to study treatment label

Drug Administration

Ribociclib should be administered as a flat-fixed dose, and not by body weight or body surface area. Patients must should be instructed to return unused study drugs to the site at the discontinuation or completion of treatment.

Ribociclib must be taken as follows:

- Patients should be instructed to take the ribociclib capsules with a large glass of water (~ 250 mL) at the same time each day.
- Ribociclib can be taken without regard to meals; however dietary habits around the time of dosing should be as consistent as possible throughout the study
- Patients should be instructed to swallow ribociclib capsules whole and not to chew, crush, or open them
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day
- Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed

Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver. Records of study medication used, dosages administered, and intervals between visits and the completion of the study will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. On PK sampling days, compliance will be assured by administration of the study treatment under the supervision of investigator or his/her designee, and will be verified by determination of ribociclib in plasma.

Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log.

Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

Human Toxicology:

As of 2 July 2013, 78 patients have been treated with increasing doses of ribociclib orally, once daily for 21 days followed by a 1 week rest (28-day cycle). Doses ranging from the starting dose of 50 mg to 1200 mg were evaluated on this schedule. In addition, continuous dosing of ribociclib at 600 mg was evaluated (once daily for 28 days of a 28-day cycle). A total of 10 events meeting DLT criteria were observed at the indicated doses and include grade 3 mucositis/stomatitis (n=1) at 50 mg, grade 3 pulmonary embolism (n=1) at 280 mg, grade 3 hyponatremia (n=1) and prolonged grade 3/4 neutropenia (n=1) at 400 mg, prolonged grade 2 elevated creatinine (n=1) at 600 mg, grade 4 thrombocytopenia (n=1) at 750 mg, grade 3 asymptomatic QTcF prolongation with grade 3 neutropenia (n=1) at 900 mg and grade 4 febrile neutropenia (n=1) and grade 4 thrombocytopenia (n=1) at 1200 mg. There was also 1 DLT, grade 3 neutropenia (n=1) at 600 mg on the continuous dosing schedule. Grade 1/2 neutropenia was observed at doses of 280 mg or higher (23%) and grade 3/4 neutropenia was seen at doses of 400 mg and higher (21%).

Asymptomatic grade 2 QTc prolongation was observed with increasing frequency starting at 600 mg with grade 3 prolongation in 2 patients. The most frequently reported AEs (> 15%) regardless of study treatment relationship include neutropenia (44%), nausea (42%), anemia (41%), leukopenia (37%), fatigue (35%), diarrhea (31%), thrombocytopenia (28%), vomiting (28%), lymphopenia (27%), decreased appetite (24%), asthenia (23%), constipation (19%), hyperglycemia (17%), and hypoalbuminemia (17%).

The majority of all reported adverse events were mild or moderate (grade 1-2) and reversible. There have been no reported deaths related to single agent ribociclib. One treatment-related death due to intracranial hemorrhage was reported in study CMEK162X2114, where ribociclib was administered in combination with binimetinib (MEK162).

Additional Dosing Guidelines for Pharmacokinetic Sampling / ECG / Chemistry panel / Lipid Panel Collection

On days with PK, ECG sampling, chemistry panel and/or lipid panel sampling, the following additional guidelines should be followed:

- On a day when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days patients may take the study treatment at home.
- Pre-dose samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the CRF. Furthermore, the dosing date and time the study medication was taken on the day before the PK assessment must be precisely recorded in the CRF.
- Post-dose PK samples should be collected after dosing of the study treatment.

7.3 Prednisone:

Pharmacology

Glucocorticoids are quickly and completely absorbed from the GI tract.

Formulation

Refer to package insert.

Storage and stability

Prednisone should be stored at room temperature.

Administration

Prednisone is administered orally.

Availability

Prednisone is commercially available, and commercial sources will be used.

Contraindications

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulosis, fresh intestinal anastamoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Immunization procedures (especially smallpox) should not be undertaken in patients on corticosteroids.

Human toxicology

Adverse affects associated with prednisone use are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, worsening of infection (i.e., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo, headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia, and arthralgia. Phenytoin, phenobarbital, and ephedrine increase metabolic clearance of corticosteroids.

Further information about prednisone can be found in the manufacturer's package insert.

7.4 Filgrastim

(Adapted from package insert- please see package insert for further details)

Formulation

Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. It has a molecular weight of 18,800 daltons. It is a sterile, clear, colorless, preservative-free liquid available

for parenteral administration. The product is available in single use vials and prefilled syringes containing either 300 mcg or 480 mcg.

Pharmacokinetics

The half-life of filgrastim is approximately 3.5 hours. It is systemically degraded.

Adverse Events

Filgrastim is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. Rare cases of splenic rupture have been reported following the administration of filgrastim. Patients who report left upper abdominal pain and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Allergic reactions to filgrastim, including anaphylaxis, skin rash, and urticaria, have been reported in postmarketing experience. The majority of reported events occurred upon initial exposure. In some cases, symptoms recurred with rechallenge, suggesting a causal relationship. In rare cases, allergic reactions including anaphylaxis, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Filgrastim should be permanently discontinued in patients with serious allergic reactions.

In the placebo-controlled trials, more common adverse events included pyrexia, bone pain, rash, cough, and dyspnea.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against filgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

Dosage and Administration

The recommended dosage of filgrastim are daily subcutaneous injections of 300 or 480 mcg depending upon body weight.

Storage and Stability

Filgrastim should be stored at 2 to 8 degrees Celsius in the carton to protect from light.

8 MEASUREMENT OF RESPONSE

8.1 Measurement of response in patients with measurable disease

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[13] Changes in only the longest diameter (unidimensional measurement- LD) of the tumor lesions are used in the RECIST criteria.

> **Note:** lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. All measurements should be taken and recorded in metric notation using a ruler or calipers. All Screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

8.1.1 Measurable disease/ Target lesions

All measurable lesions (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥10mm with spiral CT) up to a maximum of 2 lesions per organ and 5 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at Screening. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and the suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Lymph node metastases must measure 1.5 cm or greater in short axis diameter to be considered target lesions, while other target lesions must measure 1 cm or greater (with spiral CT scans).[17]

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target

	lesions, taking as reference the smallest sum LD recorded since the treatment started (including baseline LD), or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (including baseline LD)

8.1.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s), and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions

Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

8.1.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started, including baseline; see table below). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

8.1.4 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum of 12 weeks after study entry.

8.1.5 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

8.2 Evaluation of non-measurable bone disease [17]

Bone scans obtained after the Screening evaluation will be used to evaluate post-treatment changes. Bone scans obtained will be evaluated as either "no new lesions" or "new lesions" on the tumor measurement forms.

a. For the first scheduled reassessment: New lesions at the first scheduled evaluation (9 weeks) will require a confirmatory bone scan 6 or more weeks later. If no new lesions are observed on the confirmatory bone scan, study therapy is continued. If additional new lesions are observed, then the patient has experienced progression. Progression in this situation is dated as the time of the first reassessment scan.

b. For subsequent scheduled reassessments: If no new lesions are observed, study therapy will continue. If new lesions are observed, this is evidence of disease progression. Date of progression is the date at which the scan was obtained.

8.3 Post-treatment PSA Changes

All patients, with or without measurable or non-measurable disease, will be evaluated for PSA decline. Patients with disease that is not measurable will be eligible for this study and will be assessed for response based on changes in PSA and serial bone scans (if appropriate). The baseline serum PSA must be at least 2 ng/mL. Patients who show PSA increases will not be evaluated for PSA progression prior to 12 weeks of study therapy.

a. 30% and 50% PSA Decline: PSA decline of at least 30% and 50%, respectively, from baseline confirmed by a second measurement at least 3 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

b. PSA Progression: Prostate Cancer Working Group 2 (PCWG2) Criteria will be reported. PSA progression occurs when the PSA has increased 25% or greater above nadir and an absolute increase of 2 ng/mL or more from the nadir is documented. Where no decline is observed, PSA progression similarly occurs when a 25% increase from baseline value along with an increase in absolute value of 2 ng/mL or more. Patients will receive a minimum of 12 weeks of therapy prior to being evaluable for this endpoint. PSA progression (without evidence of progression on scans) will not be criteria for discontinuation of study therapy.

c. PSA Response Duration: The PSA response duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 25% above the nadir, provided that the increase in the absolute-value PSA level is at least 5 ng/mL or back to baseline, whichever is lower.

d. Progressive Disease by PSA (as defined by PSA Progression, above)

e. Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the date of the first PSA rise over the determined PSA PD value.

8.4 Progressive disease (PD)

Progressive disease will be defined by any one of the following:

1. Appearance of new metastatic lesions outside the bone
2. New metastatic lesions on bone scan confirmed as described above
3. Development of an indication for radiotherapy while on treatment
4. Unequivocal progression of non-target lesions
5. Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression

Note that PSA progression (as defined above) alone does not meet the criteria for progressive disease.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design

This is a phase 1b/II open-label study evaluating the combination of docetaxel, prednisone, and ribociclib in patients with metastatic castration resistant prostate cancer and evidence of prior progression on abiraterone, enzalutamide, ARN-509, or the combination. The phase 2 study will be a single arm two stage design evaluating the radiographic progression-free survival rate at 6 months with the treatment combination.

9.2 Determination of Sample Size and Study Power

The anticipated sample size of the phase 1b portion of the study is 9-18 patients. There will be up to three dose levels evaluated using standard 3+3 dose escalation schema. At least 6 patients must be treated at a given dose level to declare MTD. These 6 patients will be counted towards the first stage of the phase 2 study.

The sample size of the phase 2 portion of the study is based upon the anticipated radiographic progression-free survival probability after 6 months of protocol therapy. Based upon prior studies with docetaxel monotherapy, this is estimated to be 35%, accounting for the high-risk features (post abiraterone and/or enzalutamide) of this study cohort. A PFS rate at 6 months of 55% would justify further study of the treatment combination. 17 patients will be enrolled during the first stage of the phase 2 study. If at least 7 patients are free of radiographic progression at 6 months, 12 additional patients will be enrolled. If at least 14 patients are progression free at 6 months, the null hypothesis of a 35% PSA progression-free survival rate will be rejected. This design has 80% power with unidirectional level of significance of 0.1 to detect this magnitude of effect size. The study design has 62% probability of stopping early if the 6 months progression free rate is 35% or less and a 8% probability of early stopping if the progression free rate is 55% or more.

9.3 Accrual

For the Phase 1b portion of the study, it is estimated that approximately 2 patients per month will be enrolled, and that the recommended phase 2 dose of ribociclib will be established 12 months after first patient enrolled. During the Phase 2 portion of the study, it is estimated that approximately 2 patients per month will be enrolled, leading to an estimated accrual period during phase 2 of approximately 15 months.

9.4 Interim Analyses

During the phase 1b portion of the study, if dose level IB (weekly docetaxel 30 mg/m^2 in combination with ribociclib 200 mg/day) is declared a non-tolerable dose, the study will close to further accrual.

During phase 2, an interim analysis for safety and efficacy will be conducted after 17 evaluable patients have been enrolled. If six or more patients experience toxicity meeting the definition of dose-limiting toxicity, study accrual will be halted and alternative dosing schema may be pursued. If less than 7 out of the first 17 patients enrolled are radiographically free of progression 6 months from the start of protocol therapy, the study will halt accrual and alternative dosing schema may be pursued.

9.5 Analysis Population

Subject disposition and all efficacy endpoints will be assessed using data from the intent-to-treat population. Safety analysis will include all patients who receive at least one dose of protocol therapy.

9.6 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, and baseline height and weight. Additional disease specific features will be captured on electronic case report form, including:

- Gleason grade at the time of diagnosis
- Year of prostate cancer diagnosis
- Extent of disease at the time of study entry (nodal, bone, visceral metastases (lung, liver, or both)).
- Duration of response to primary androgen deprivation therapy
- Type of resistance to prior abiraterone/enzalutamide/ARN-509 (primary = no PSA decline or radiographic response; secondary = all others)
- Prior chemotherapy in the hormone-naïve setting (yes/no), and if yes, date of last chemotherapy administration

9.7 Study Endpoints

9.7.1 Primary Endpoints

Phase 1b: Maximally tolerated dose and recommended phase 2 dose of ribociclib in combination with docetaxel plus prednisone, based upon evaluation of dose-limiting toxicities and adverse events measured using Common Toxicity Criteria version 4.03

Phase 2: Radiographic progression-free survival rate at 6 months from start of protocol therapy.

9.7.2 Secondary Endpoints:

- Median radiographic progression-free survival
- Objective response rate and median duration of response using RECIST 1.1 criteria, among patients with measurable disease at baseline
- PSA progression-free survival (defined in Section 8)
- PSA response rate (defined in Section 8)
- Adverse events of the treatment combination using Common Toxicity Criteria version 4.03
- Pharmacokinetic profile of ribociclib when given following administration of docetaxel and with concurrent prednisone use. PK parameters to be measured include estimated Cmax, AUC0-24, and Css.

9.7.3 Exploratory Endpoints:

- Association between clinical outcomes on ribociclib plus docetaxel with baseline and percent change from baseline in SUVmax-ave on gallium citrate PET/CT (Optional - UCSF Patients Only)
- Association between clinical outcomes and genomic markers of MYC/cell-cycle pathway, including MYC amplification/overexpression, validated MYC gene expression signature score, Rb1 deletion, CDK4/6 and cyclin D overexpression, assessed via metastatic tumor biopsy and CTCs and cell-free ctDNA
- Pathway signature of clinical, genomic, and proteomic factors predicting sensitivity to treatment combination using an unbiased approach with DiPSC bioinformatics tool

9.8 Methods for Analysis

9.8.1 Analytic plan for the primary study endpoints

The maximum tolerated dose and recommended phase 2 dose of ribociclib in combination with docetaxel and prednisone will be determined using criteria outlined in Section 6. The frequency and severity of adverse events will be reported in descriptive fashion.

For the phase 2 portion of the study, the radiographic progression-free survival rate at 6 months and median radiographic progression-free survival will be estimated using the Kaplan-Meier product limit method. Durations will be measured from day 1 of study treatment to first date of radiographic progression or death, whichever occurs sooner. Patients who discontinue study therapy for toxicity, withdrawal from study, or PSA-only progression, will be censored at the date of last radiographic tumor assessment for this analysis. Patients who discontinue therapy for evidence of clinical progression/clinical deterioration will be included in this analysis.

9.8.2 Analytic plan for the secondary study endpoints

For patients with measurable disease at baseline, the objective response rate will be descriptively reported. Among patients with objective response, the median duration of response will be estimated using the criteria outlined in Section 8.1.5.

The proportion of patients with greater than 50% decline from baseline in serum PSA will be reported in descriptive fashion. The probability distribution of the median time to PSA progression will be estimated using the Kaplan-Meier product limit method. Durations will be measured from day 1 of study treatment to first date of PSA progression, as defined in Section 8. Patients who discontinue study therapy prior to PSA progression will be censored at the date of last PSA assessment while receiving protocol therapy.

The incidence and severity of adverse events related to treatment regimen will be descriptively reported using Common Toxicity Criteria version 4.03.

The estimated $AUC_{0\text{-}24hr}$, Cmax, and Cstead-state serum concentration of ribociclib will be reported using descriptive statistics.

9.8.3 Analytic plan for the exploratory study endpoints

Gallium citrate PET imaging (Optional - UCSF Patients Only):

A trained nuclear medicine physician blinded to the clinical outcomes of the patients will evaluate the reconstructed PET, CT, and fused PET/CT images using a PET volume computer-assisted reading software package. A positive lesion on gallium citrate PET will be defined as a focus of activity with at least 1.5 times higher SUV compared with mediastinal blood pool that is not attributable to other etiologies of tracer distribution (e.g. inflammation, excretion). A volume of interest (VOI) will be semiautomatically placed around each lesion, and the calculated maximum standard uptake value (SUVmax) will be recorded for each lesion. Adjusted SUVmax data will then be averaged across all lesions within a given patient (SUVmax-avg). In order to avoid clustering effects, analysis will be limited to the five largest osseous metastases and all visceral metastases.

For the purposes of analyzing the association between SUVmax-ave and percent change from baseline on the paired scans respectively with subsequent clinical outcomes, the phase 2 cohort will be dichotomized into those with SUVmax-ave values above and below the median. The dichotomized subgroups will be compared with respect to objective response rate and PSA response proportion using Fisher's exact test, and the log-rank test will be used to compare dichotomized groups with respect to radiographic progression-free survival and time to PSA progression.

Genomic predictors of response:
MYC amplification, overexpression, and signature score using a validated MYC expression signature, along with other markers of MYC/cell cycle proliferation, including Rb1 copy number/mutation status, CDK4/6 and cyclin D/E expression, will be ascertained using metastatic tumor biopsy, and whenever possible, from concurrent analysis of CTCs and cell-free ctDNA. The association between these variables and clinical outcomes will be performed using Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables.

No adjustment for multiple comparisons will be made for this exploratory study analysis.

DiPSC-generated signature of response:
The study cohort will be dichotomized into those with either objective tumor response or clinical benefit from combination therapy (stable disease or greater for more than 6 months) versus those that do not have clinical benefit. The DiPSC tool integrates all measured clinical, genomic, and proteomic factors in an unbiased manner to determine those factors most tightly correlated with clinical benefit/response or resistance to protocol therapy. Those factors will be utilized to develop a 'signature' of benefit from taxane + CDK4/6 inhibitor combination therapy.

10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

U.S. regulations require that a sponsor reports Serious Adverse Events (SAEs) occurring with use of its product in a clinical trial if it is unexpected and felt to be related to use of the drug. All SAEs that occur will be evaluated by the site investigator and confirmed by the Lead Site Sponsor/Investigator for reportability to FDA. The PCCTC will facilitate this evaluation with the site investigator and Lead Site Sponsor/Investigator. An Adverse Event should be identified, Serious Adverse Event and Expectedness determined and causality assessed by the investigator using the definitions that follow.

10.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment.

A **Serious Adverse Event (SAE)** is an adverse event occurring at any dose that results in any of the following outcomes:

a. Death
b. Life-threatening[1]
c. Persistent or significant disability/incapacity[2]
d. In patient hospitalization or prolongation of existing hospitalization
e. Congenital anomaly/birth defect

1 The term "life-threatening" in the definition of "serious" refers to an event in which in the view of the initial reporter the patient was at immediate risk of death from the adverse experience as it occurred; it does not refer to an event which had it occurred in a more severe form, might have caused death.

2 A substantial disruption of a person's ability to conduct normal life functions.

An event may not meet any of the above seriousness criteria but still be judged as medically serious. That is, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes (a-e) listed above. Some examples of this type of event are:

- blood dyscrasia without inpatient hospitalization
- convulsions without inpatient hospitalization
- intensive treatment in an emergency room or at home for allergic bronchospasm without inpatient hospitalization
- development of drug dependency
- drug abuse
- overdose with an associated serious event, or required intervention to prevent impairment/damage

An **Unexpected Adverse Event** is not listed in the current US Package Insert (USPI) or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Causality is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an adverse event. It includes assessing temporal relationships dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) or a lack of one or more likely causes.

The Investigator must determine if an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

Unlikely:
The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug.

Possible:
The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug *BUT* the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication

Probable:
The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition *or* the event cannot be the effect of a concomitant medication

Definite:
The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug

Unknown:
Based on the evidence available, causality cannot be ascribed

11 DATA SAFETY MONITORING PLAN

The UCSF Helen Diller Family Comprehensive Cancer Center (UCSF-HDFCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-HDFCCC institutional clinical studies. PCCTC will facilitate this responsibility. A summary of DSMC and PCCTC activities for this study includes:

DSMC:

- Review of subject data in each cohort
- Approval of dose escalation by DSMC Chair (or qualified alternate)
- Monthly monitoring (depending on study accrual)
- Review of suspected adverse reactions considered "serious"
- Minimum of a yearly audit

PCCTC:

- Weekly UCSF Site Committee Meetings: PCCTC will generate the necessary report and participate in the meeting and document minutes as necessary.
- UCSF DSMC Reports every 6 weeks: PCCTC will generate the report (in a format agreed upon at the onset of the protocol) and provide to Study Chair to submit to DSMC.
- Bi-Weekly Conference Calls with Participating Sites: PCCTC will coordinate, schedule, provide reports for this meeting in a format agreed upon at the onset of the protocol as well as participate and take minutes.
- PCCTC will perform monitoring per the Monitoring Plan (MP) and Data Management Plan (DMP) and these reports will be submitted to the Study Chair to submit to the DSMC.
- PCCTC will monitor grade 3 or 4 adverse events and report to the Study Chair if the incidence of adverse events are above the range stated in the IB so that the Study Chair may report this information to the DSMC.
- PCCTC will maintain an electronic regulatory binder for each of the participating sites and supply documentation to UCSF as needed.

11.1 Monitoring and Reporting Guidelines

All institutional Phase 1 therapeutic studies are designated with a high risk assessment. The data is monitored monthly as subjects are enrolled and includes all visits monitored up through the Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report generated by PCCTC will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and suspected adverse reactions considered "serious," and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within 2 business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's decision, further study accrual is held while further investigation takes place.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at weekly UCSF Site Committee meetings. PCCTC will generate any necessary reports and participate in the meeting as necessary. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

Dose Level Considerations

The PI/Study Chair, participating sites, investigators, and research coordinators will review enrollment for each dose level cohort during the weekly site committee meetings. The dose level for ongoing enrollment will be confirmed for each subject scheduled to be enrolled. Dose level assignments for any subject scheduled to begin treatment must be confirmed with Principal Investigator.

The DSMC will be responsible for monitoring all data entered in Medidata Rave®. Approval for dose escalation must be obtained from DSMC chair.

11.2 Review and Oversight Requirements

11.2.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into Medidata Rave®.

All clinically significant adverse events entered into Medidata Rave® will be reviewed on a weekly basis at the UCSF Genitourinary Oncology Site Committee. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s). The weekly reports for this meeting will be prepared by PCCTC. In addition, all suspected adverse reactions considered "serious" are entered into Medidata Rave® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks. The report for this meeting will be prepared by PCCTC and submitted to the DSMC by the Study Chair.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee and PCCTC [redacted] must be notified within 24 hours of knowledge of the event from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

11.2.2 Serious Adverse Event Reporting: UCSF Requirements

Serious Adverse Event reporting will be facilitated by PCCTC in accordance with the UCSF Institutional Review Board(IRB) Regulations and Food and Drug Administration (FDA) guidelines.

UCSF IRB website for guidance in reporting serious adverse events:
http://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

For clinical trials conducted under an IND, SAE reporting will in accordance with Code of Federal Regulations Title 21 volume 5 Part 312 subpart B (21CFR312.32):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

SAEs will be reported on a MedWatch form. A copy of the MedWatch report must be sent to the DSMC [redacted]. The date the SAE was sent to all required reporting agencies will be documented in the EDC. Hard copies of the report will be maintained in the regulatory files.

If the SAE is death and determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to PCCTC [redacted] and the DSMC Chair or his designee within 24 hours of becoming aware of the event. This will be done by personal communication via phone or in person. The reporting investigator will confirm the verbal communication via e-mail and will copy the e-mail to the DSMC Administrator.

If the above action occurs in a multiple-institutional clinical trial coordinated by UCSF, PCCTC will insure that all participating sites are notified.

11.2.3 SAE Reporting: Novartis Adverse Event Reporting Requirements

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form), if applicable.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department [redacted] within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.
If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators.

Pregnancies
To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis Oncology Drug Safety and Epidemiology Department (DS&E) [redacted] Pregnancy follow-up should include an assessment of the possible relationship

11.2.4 Review of Adverse Event Rates

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will be generated by PCCTC and indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within **1 business day** via e-mail. The DSMC must receive a formal letter within **10 business days** and the IRB must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]
Phone: [redacted]
Email: [redacted]
Address: [redacted]
UCSF
San Francisco, CA 94158

DSMC Monitors

[redacted]
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA 94143

12 DATA MANAGEMENT

This study is a multi-institution, investigator- sponsored trial (IST) coordinated by UCSF and the Prostate Cancer Clinical Trials Consortium (PCCTC). The Principal Investigator at UCSF holds the role of Study Chair.

The Principal Investigator and/or PCCTC is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Participating sites will prepare and maintain adequate and accurate case histories as per their standard institutional guidelines. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

Study drugs will be shipped from the drug manufacturer directly to the site for direct distribution of the drugs to the study patients. Each site will be responsible for drug accountability at their site.

Approval of Protocol and Amendments

All protocol amendments must be approved by the participating site's IRB within 90 days of receipt. Failure to do so may result in the suspension of study activities at that site.

Upon approval of the protocol or amendment by a participating site's IRB, a copy of the approval documentation must be submitted (electronic or hardcopy) to PCCTC. PCCTC will inform the Study Chair.

Data Submission

Standardized eCRFs and completion guidelines will be created by the PCCTC for the collection of all study data. Access and training for Medidata Rave will be made available to participating sites upon local regulatory approval. The participating site PI is responsible for ensuring eCRFs are completed accurately and in a timely manner.

All participating sites will be granted access to Medidata Rave and will be expected to enter data as described in the Medidata Rave Data Guidelines provided by PCCTC.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Protocol Review Committee

This study will be reviewed by the UCSF Comprehensive Cancer Center Protocol Review Committee (PRC) for scientific merit. After initial review and approval, the study will be reviewed at least once a year for scientific progress. Any changes to the protocol are to be reviewed and approved by the PRC.

Participating sites will review this study as per their standard scientific review and approval process.

13.2 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The study will be reviewed by the IRB. After initial review and approval, the study will be reviewed at least once a year as per FDA regulations (21 CFR 56.109). Any changes to the protocol and consent form are to be reviewed and approved by the IRB. Participating sites will review this study as per their standard IRB/IEC review and approval process.

It is the responsibility of the Principal Investigator to keep the IRB informed of the progress of the study, including changes to the protocol or consent form, exceptions or deviations from the protocol, and any new developments which may affect subject safety or willingness to participate.

13.3 Investigational New Drug Application (IND)

IND application will be filed and approved with FDA prior to study initiation.

A copy of all FDA correspondence will be maintained by the centralized regulatory staff of the UCSF-HDFCCC and PCCTC. It is the responsibility of the Study Chair to forward any correspondence concerning the IND and FDA to the centralized regulatory staff and PCCTC.

13.4 Conduct of the trial

The investigators will obtain informed consent and will conduct the trial in accordance with Federal regulations, institutional requirements, and the Declaration of Helsinki.

Role and Responsibilities

Sponsor Investigator

The Sponsor Investigator is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of SAEs
- Reviewing data from all participating sites

PCCTC (Prostate Cancer Clinical Trials Consortium)

The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration

- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- Electronic Data Capture (EDC) system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AEs and SAEs to the PCCTC and UCSF as outlined in Sections 10 and 11
- Reviewing SAEs and facilitating regulatory reporting in coordination with Sponsor-Investigator.
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating monitoring by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, the guidelines of GCP, and applicable Standard Operating Procedures (SOPs).
- Registering all patients with the PCCTC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

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APPENDIX 1: ECOG Performance Status Scale

DESCRIPTION	SCALE
Normal Activity	0
Symptoms of disease, able to carry out activities of daily living	1
Out of bed >50% of time; occasionally needs help	2
In bed >50% of time; needs nursing care	3
Bedridden; may need hospitalization	4

APPENDIX 2: List of Prohibited Medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or ribociclib.

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362. pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (https://crediblemeds.org/). Please contact the medical monitor with any questions.

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycinvoriconazole
Strong CYP3A4/5 inducers	carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacine, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
Other investigational and antineoplastic therapies not part of the study	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, all SERMS (including raloxifene) biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.
Herbal preparations/ medications	Herbal preparations/medications that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These herbal medications include, but are not limited to: black cohosh, St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes). or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of January 2018.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org.

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University “Clinically Relevant” Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

APPENDIX 3: List of Medications To be Used With Caution

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir[5], modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates1	Alpha-dihydroergocryptine, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine,rifamycin, simeprevir, telmisartan,timcodar, troglitazone, valinomycin, velpatasvir
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium, and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, tipiracil/trifluridine, tizanidine, tolterodine, toremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone

1 Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
2 The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.
3 MATE1 and MATE2 share considerable substrate specificity.
4 OCT1 and OCT2 share considerable substrate specificity.
5 Lopinavir is prohibited when combined with ritonavir (see Table 14-1)

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University “Clinically Relevant” Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

APPENDIX 4: Pharmacokinetics (PKs) Collection Instructions (Phase 1b only)

Please see separately attached Appendix 4.

APPENDIX 5: Plasma/Serum/Peripheral Blood Mononuclear Cell (PBMC) Banking (Optional)

Please see separately attached Appendix 5.

APPENDIX 6: Circulating Tumor Cells (CTCs) and Cell-Free Circulating Tumor DNA (ctDNA) Collection and Processing Instructions

Please see separately attached Appendix 6.

APPENDIX 7: Tumor Biopsy Procedure (Optional)
Please see separately attached Appendix 7.

APPENDIX 8: ECOG/KPS Conversion Scale

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead